Challenges of the current medicine

Elżbieta Krajewska-Kułak, Wojciech Kułak,
Cecylia Łukaszuk, Jolanta Lewko, Mateusz Cybulski

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Learn from yesterday, live for today, hope for tomorrow.
The important thing is not to stop questioning
Albert Einstein

Dear Colleagues

The monograph periodical "*Challenges of the Current Medicine - 10 Edition"* is a collection of authors from many different medical centers.

Medicine is changing more and more every year. Despite the enormous technological progress, modern medicine is still unable to cope with all diseases. The use of modern and less and less invasive treatment methods cannot help every patient anyway. How long has it been since the time of Hippocrates. They show impressive achievements in transplantology, laser corrections, titanium hip joints, laparoscopic surgery or in vitro fertilization…. Unfortunately, the never-ending pursuit of perfection continues. We are entering the world of genetic manipulation more and more boldly. What is next? In which medical areas are we most eagerly awaiting breakthroughs? According to UN forecasts, by 2025, 11%. Of the world population (21% in the case of Europe) will be people over 65. According to the International Diabetes Federation, the number of people suffering from diabetes, for example, is to increase to 578 million by 2030 and to 700 million by 2045. According to Deloitte experts, in the coming years, the medical industry will focus on such trends as aging societies, an increase in budget spending on health care, the popularity of health and fitness applications, the use of telemedicine and virtual diagnostics, the spread of civilization diseases and antibiotic resistance. It is estimated that by 2025 in medicine, there will be a fundamental change in priorities and decision-making methods regarding the recommended treatment and a reevaluation of the approach to diagnostics. According to the idea of "4P" (predictive, preventative, personalized, participatory), medicine should be predictive, preventive, personalized, and participatory. Thanks to the use of the latest technological achievements in data set analytics, genomics, artificial intelligence, nanotechnology, quantum computers, or 5G communication. It will be possible to diagnose faster and better adapt it to patients' individual needs and conduct research and development procedures more efficiently.

The outbreak of the pandemic, in turn, triggered a dynamic acceleration of the digital transformation of the medical sector, which within nine months reached levels expected in the next many years. The pandemic also highlighted the importance of a wide range of cooperation in mobilizing and coordinating public and private efforts to tackle global health threats.

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CHALLENGES OF MODERN MEDICINE

How do we gain knowledge about health? - on the trail of modern medicine traps

Monika Tokarczyk[1], Maciej Kloc[1], Patrycja Madejska[1], Szymon Wiśniewski[2]

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Abbreviation list

- EBM - Evidence-Based Medicine
- HCPs - Healthcare Professionals
- OTC - Over the Counter
- POM - Prescription Only Medicine
- SM - Self Medication

  NSAIDs - Nonsteroidal Anti-Inflammatory Drugs

  PPIs - Proton Pump Inhibitors

Introduction

What does being healthy mean? Answering that question seems to be easy. But is it? According to the World Health Organization, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Years pass by, and the definition stays almost unchanged. What changes is people's health awareness and willingness and ability to maintain their health? Health maintenance includes necessary treatment, following medical recommendations, prevention, and health promotion.

Respondents' answers about caring for their own health would probably be simultaneously similar and different from each other. The basic similarity- wish of being healthy. The basic difference - the way of achieving it. The differences result from individual variability and life experience, but what they also show is a wide variety of ways of gathering and verifying information. The verification process is crucial for not getting lost in a huge avalanche of information that people are bombarded with. In the present world, it is effortless

to collect information. In 2019, over three-quarters of households in Poland had broadband access to the Internet at home, and 78.3% (the tendency is growing) of persons aged 16–74 used the Internet regularly [1]. The difficult part is to judge which information is valuable, trustworthy, and without fake marks. What may also be complex is to catch the right moment to give up on tempting self-treatment based on the media and commercials and give yourself into the hands of specialists.

The development of information technology and medicine and their mutual interaction undeniably opened new possibilities for patients and healthcare representatives. However, on the other hand, there is an ever-growing danger of an outbreak of fake news epidemic and devaluation of medical authorities.

Aim of the publication

This publication aims to find out the primary sources of knowledge about health in general, the level of obedience to the medical recommendations, and the position of healthcare representatives at times of broad access to any information.

Methods & research material

The material of the study includes a summary of the results of the online survey named 'How do we gain health knowledge?'. The survey was prepared using Google Forms by the authors of this publication. It was aimed at the population of Polish teenagers and adults at different levels of education, professionally involved and uninvolved in medicine. Two hundred sixty-seven results were collected. The questionnaire filling was voluntary and anonymous. Data were analyzed using the Google Sheets program.

Results

The results presented below are based on data gathered in the Internet survey. Each response was complete and thus taken into account in the analytic sample.

The vast majority of respondents were in the age group between 19 and 25 years (56.6%); the second biggest group were people between 26 and 35 years (18,7%).

The smallest group of survey respondents were people over 60 years of age (0,4%) [Fig.1].

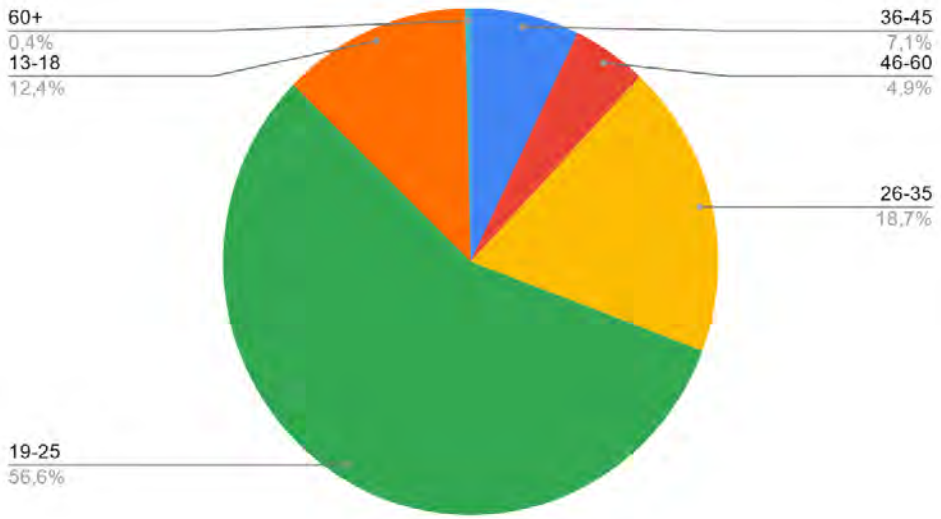


Figure 1. Age respondents

As presented in Figure 2, over eighty percent of the respondents identified themselves as women (83,1%), and 16.9% identified as men.

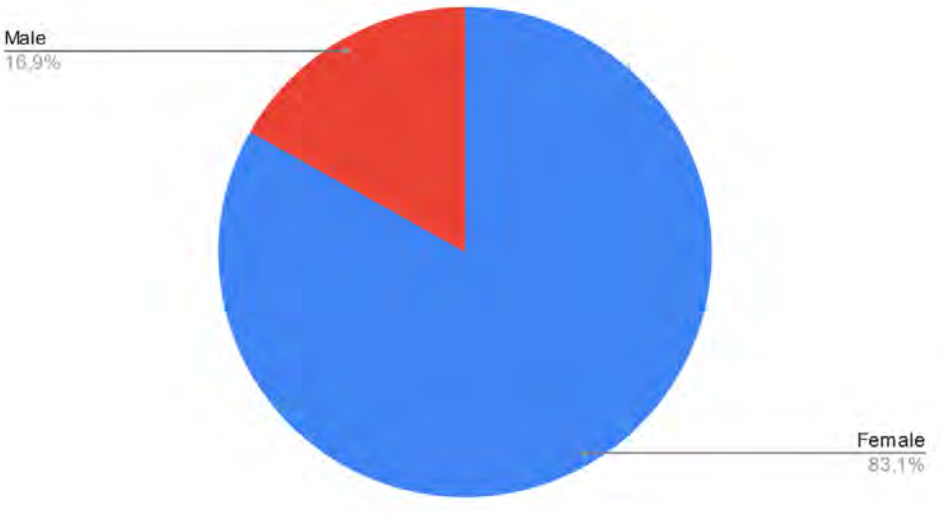


Figure 2. Gender respondents

In educational background, over 40% of interviewees were in the course of study, 34,6%

had a higher education, 12,4% had secondary education, 11,5% received an elementary education, and the smallest group, 1,4% have vocational education [Fig. 3].

The majority of respondents are neither professionally connected with healthcare nor studying medical subjects - 30,7%, the remaining part is career-wise connected with healthcare 69.3% [Fig. 4].

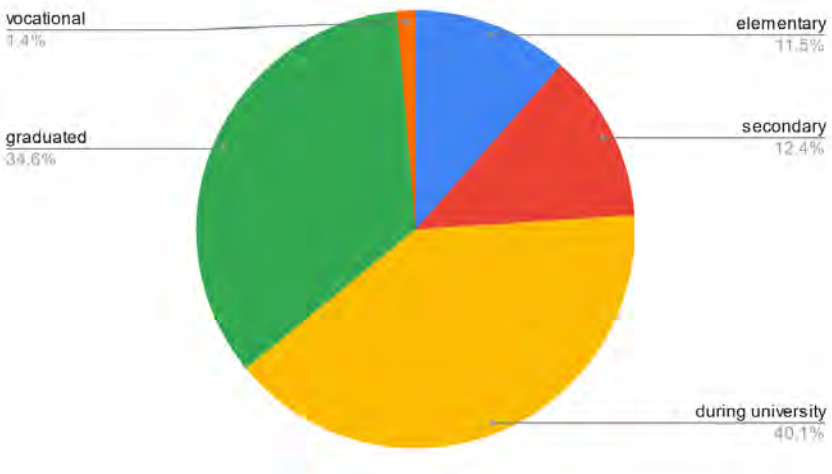


Figure 3. Education respondents

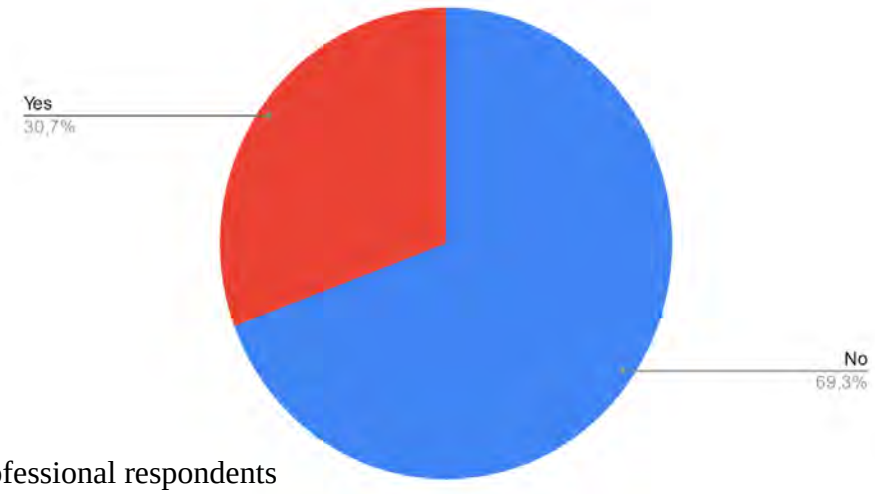


Figure 4. Professional respondents

In a multiple-choice question concerning sources of knowledge about health the biggest part of respondents - 80,9% claim that they are basing their knowledge on the information from the medical doctors. The second place is taken by the medical portals, such as mp. pl, the most famous Polish website dedicated to doctors and patients (54,7%). After that, medical doctors'

profiles on social media were chosen as the source of knowledge (42,3%). The following responses presented as follows: friends – 27.3%, Internet groups and forums (26.6%), Wikipedia (22,1%), YouTube (16.5%), TV shows (15.4%), and mobile medical apps (6.7%) [Fig. 5].

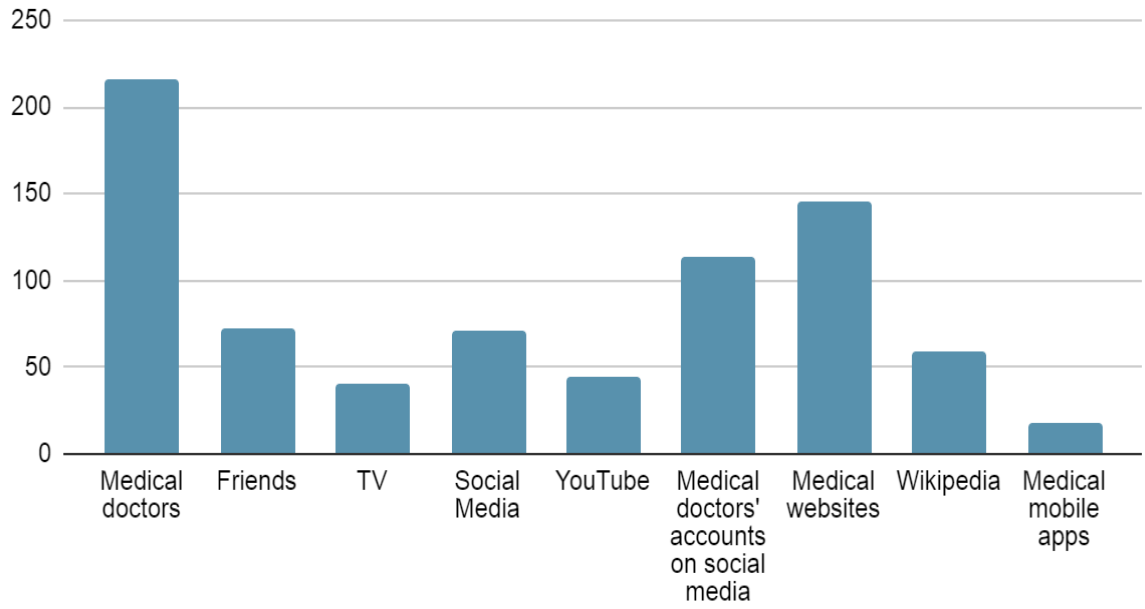


Fig. *5*. Information sources

Most interviewees (66.3%) claimed they bought and took OTC medications or supplements without medical consultation at least once [Fig. 6].

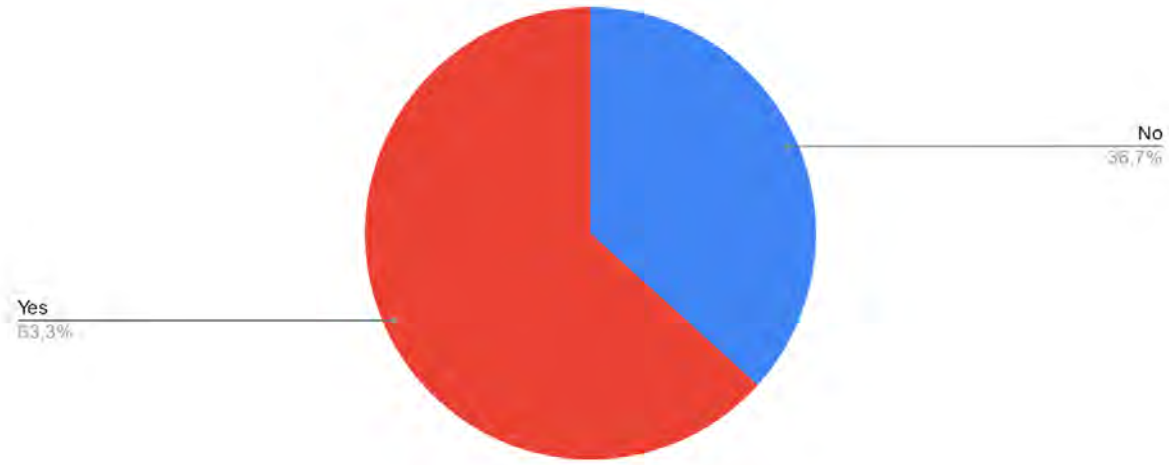


Fig 6. Purchase of OTC drugs

39% answered that they had used a POM from their domestic first-aid kit without medical consultation, which was initially prescribed for somebody else [Fig. 7].

13,9% have taken another person's POM that they use for their diagnosed disease without medical consultation [Fig. 8].

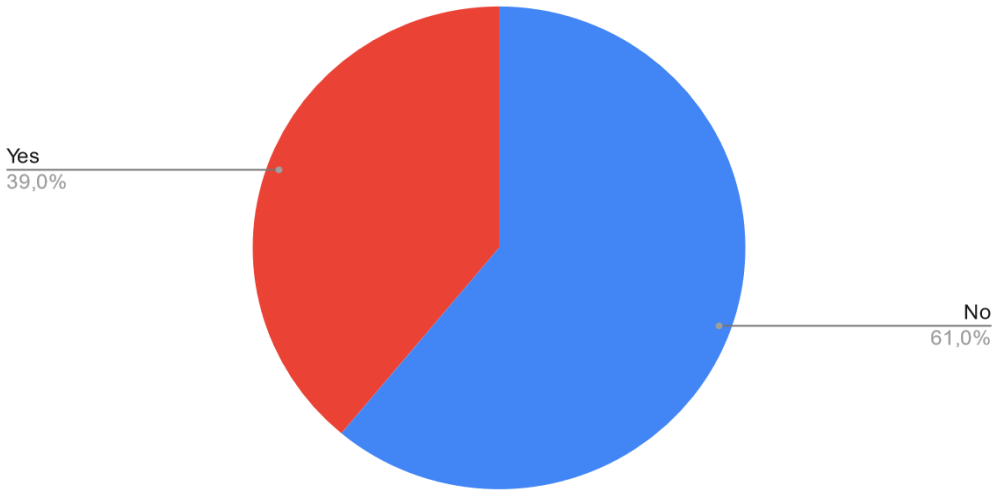


Figure 7. Have used a POM from their domestic first

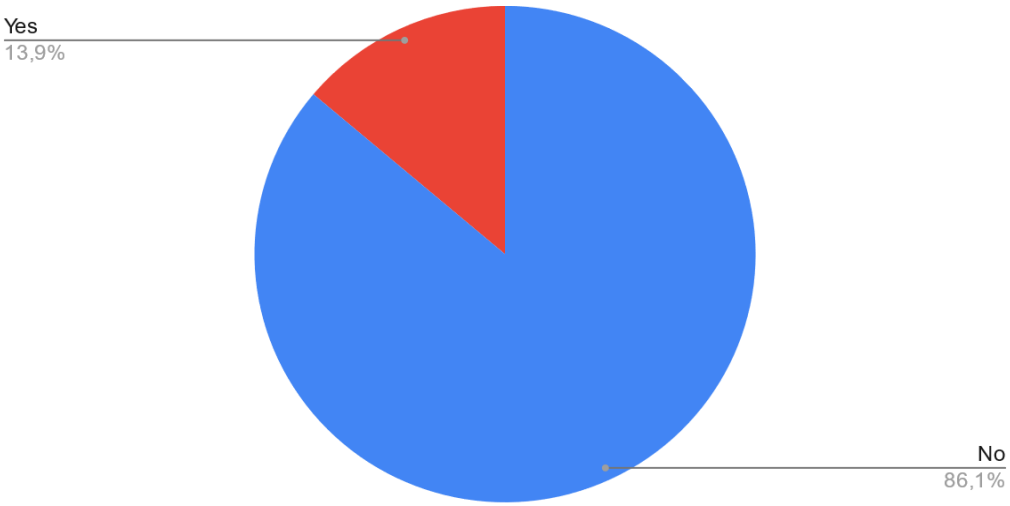


Figure 8. Using the help of another person

Regarding vaccinations, 37,1% of our respondents are fully vaccinated, including prophylactic vaccinations that are not mandatory (e.g., the flu), and are willing to vaccinate their children. 55.4% are fully vaccinated and are willing to vaccinate their children, but they have not taken prophylactic vaccinations that are not mandatory [Table I].

6.7% of the group are not vaccinated and unwilling to vaccinate their children, and the smallest group (0,7%) are vaccinated but unwilling to vaccinate their children:

	Medical professionals (82)	Non-medics (185)
Attitude to vaccination		
I'm not vaccinated and I would never vaccine my child	7,3%	6.5%
I'm vaccinated, but I would never vaccinate my child	-	1,1%
I'm vaccinated and I would vaccine my child, but I'm not vaccinated for influenza	51,2%	57,3%
I'm vaccinated and I would vaccine my child and I'm vaccinated for influenza	41,5%	35.1%
COVID-19 vaccine		
I don't want to get vaccinated and I discourage other people	14,6%	40,5%
I would like to get vaccinated, but the doctor decided there are some contraindications	1,2%	1,6%
I would vaccinate as soon as it would be available for me	20,7%	51,9%
I'm vaccinated (at least one dose)	63,4%	5.9%
Have you ever taken any medicine or supplement based only on the information found on the Internet without consultation with a doctor or pharmacist?		
YES	65.9%	62,2%
NO	34,1%	37,8%
Have you ever taken any prescription drugs that you already owned without any consultation with a doctor or pharmacist?		
YES	42,7%	37,3%
NO	57,3%	62,7%
Have you ever taken any prescription drugs that you get from someone without any consultation with a doctor or pharmacist?		
YES	17,1%	82,9%
NO	12,4%	87,6%

As it comes to vaccinations against SARS-CoV2 causing COVID-19 disease the biggest part of the group is willing to take the vaccine as soon as it will be possible (42,3%), 23,6% are vaccinated at least with one dose and 1,5% is willing to take the vaccine but they have health contraindications confirmed by a medical doctor. 18,7% are not willing to take the vaccine and are discouraging their relatives to do so, 13,9% are not willing to take the vaccine but they are encouraging their relatives to take it.

It should be mentioned that the data was collected to date 28-05-2021 and most of the answers were uploaded when vaccinating was not available for the full population [Table I).

Most interviewees (86.1%) declare paying attention to the source of overheard information or the one read on the Internet [Fig. 9].

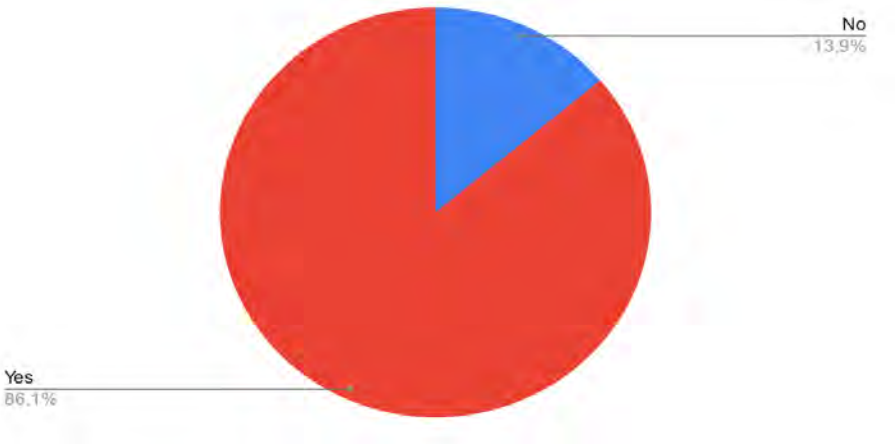


Figure 9. Internet as a source of information

When it comes to Google searching (43,1%) chooses the most popular sites offered by Google, and (56.9%) read information only from websites of their choice [Fig. 10].

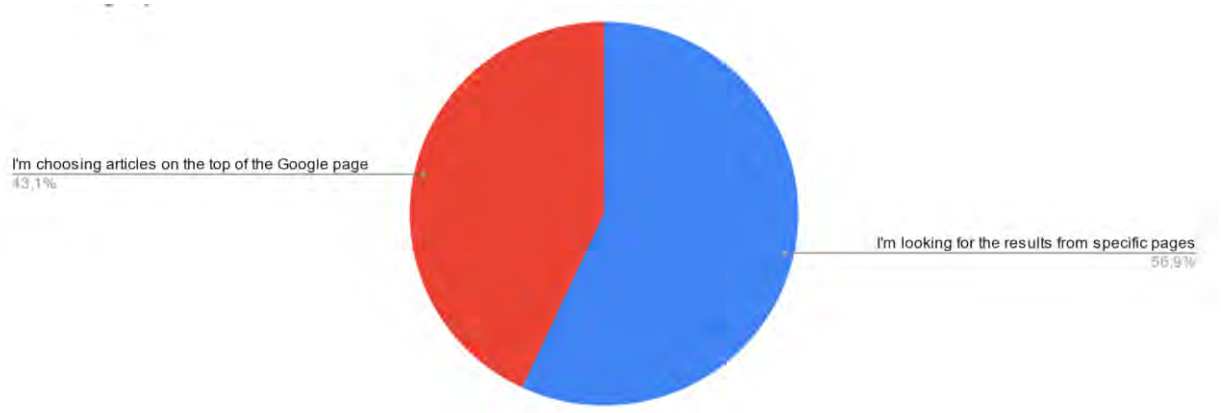


Figure 10. Internet as a source of information

The majority of respondents (87,6%) verify the information in a couple of different sites while 8,2% check the content in two sources and 4,2% only in one source [Fig. 11].

56.2% of interviewees claimed that they check their symptoms on the Internet before going to the doctor. When their diagnosis is different from the medical doctor's one, 92,5% of them are marked in a multiple-choice question that they abide by the doctor's recommendations. 11.2% do not accept the recommendations they do not agree with and search for another doctor, 3.4% do not agree at all with the doctor's recommendations and abide by the information they found on the Internet and 1.1% do not accept the doctor's recommendations and end the diagnostic process at this point.

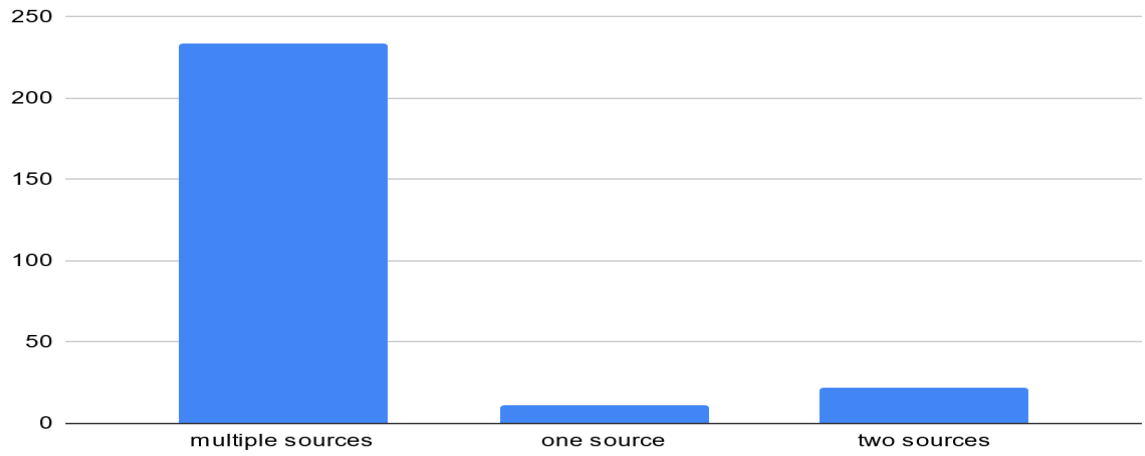


Figure 11. Main sources of information

36.3 percent declare that the information found on the Internet at least once rendered that they forwent going to the doctor [Fig 12].

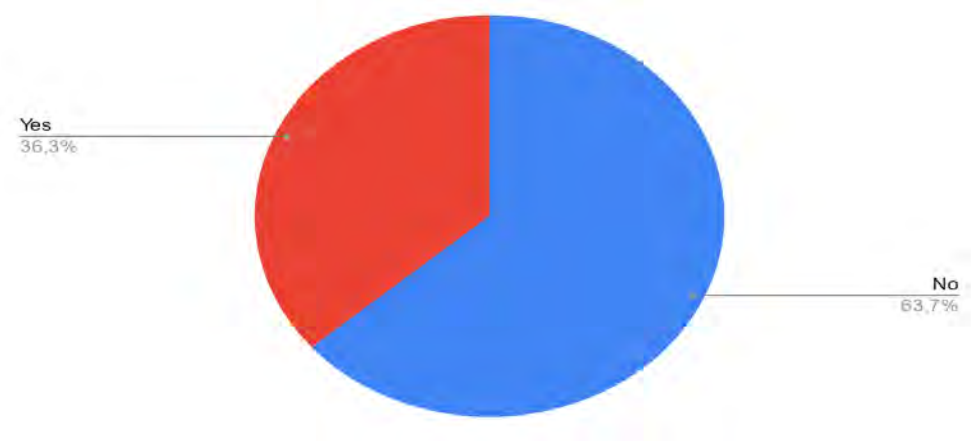


Figure 12. Information found on the Internet and resignation from visiting a doctor

8,2% answered that they witnessed a situation when the information gathered on the Internet caused side effects. 36% declare that at least once, the information they found on the Internet was verified by the person with medical education as fake. Most of those who experienced such a situation rejected that information and agreed to the recommendation verified as true, 20,7% of this group sometimes did not want to trust the medical worker and partially stayed true to the information found by themselves and 4,4% did not accept the information verified as fake at all.

70,8% of the interviewees claim that they understand the term "Evidence-based medicine".

Discussion

Recent years showed that the growing access to many sources of information leads to the indisputably valuable tendency - growth of interests in healthcare among people [10]. What seems to be the leading problem connected with that change is a huge overload of information from many sources - some of them being valuable medical publications, some, however, presenting a subjective point of view of the author not related to the medical environment or even without basic medical education. Above that, another problem is the misinterpretation of those texts by the readers and the lack of need to verify gathered knowledge with medical workers. It is not easy not to get lost. Internet use for health-related purposes and self-medication are common public health problems. Our study confirms that the most preferred sources of information are those from medical doctors [Fig. 5]. The Internet has promising potential to support patients and keep them informed about health, but there is a significant risk of erroneous advice that may be found online. There are no strict regulations to prevent misinformation. Medical professionals should provide patients with the concept of 'evidence-based medicine' to deliver them trusted sources of knowledge [2,3,4].

Our research study showed two main observations - inequality of the responses to questions regarding healthcare between medical and non-medical interviewees and weakening of trust towards medical workers. The first result listed is inseparably connected to the knowledge about health gained in a medical university and further practice. The second aspect is much more complicated. One of the reasons causing the weakening of trust can be the construction of the Polish healthcare system where there are few doctors for the number of citizens, and the patient is forced to wait in lines for months to get a consultation with

a specialist. This also leads to the searching for information on one's own other than listening to the doctor's orders - respondents of our survey that declare buying and taking OTC medications or supplements without medical consultation, using a POM from their domestic first-aid-kit without medical consultation, which was originally prescribed for somebody else or taking another person's POM that they use for their diagnosed disease, without medical consultation are mainly those from the non-medical environment [Table 1].

In developing countries, self-medication is often unavoidable. Developing countries have less access to health services, and it is a cheaper solution. Some OTC drugs can be purchased at grocery stores, gas stations, etc. Store employees often do not have proper knowledge about products and diseases processes. This can lead to complications induced by drug interventions due to medicines interaction, inadequate dose, and route of administration [5.6]. One of the most dangerous effects of self-medication is antibiotic resistance [7]. Also, NSAIDs, one of the most commonly used medications, can cause ulcers and bleeding as patients do not know about protective drugs, such as PPIs [8]. SM can also provide benefits such as increased access to medication, lowering the costs of the community. Limited health education is a factor that is a source of inefficiency. Country authorities should implement new policies to solve these problems.

As told above it is extremely important that in the era of broad access to information healthcare workers should provide evidence-based medicine. Our respondents claim to understand the term EBM in over 70%. However, we cannot forget that to understand is one thing, to put it into practice is another.

Our study shows that respondents pay attention to the source of information they read [Fig. 9]. Moreover, they try to verify them using multiple websites. As mentioned before, the verification process is essential for finding valuable information. At the same time, we cannot ignore the fact that above 40% of interviewees still prefer to read sites that have the best positioning in Google rather than to choose their preferred sites [Diagram 10]. Google does not arrange results in accordance with scientific evidence but in accordance with click rates. It is a risk factor for gathering fake information. According to studies, falsehood is more clickable and diffuses farther, faster, deeper, and more broadly than the truth in all categories of information [9]. It is significant considering the fact that more than half of respondents claim to check their symptoms on the Internet before going to the doctor. What is more, 36% of respondents claim that they replaced their medical consultation with their research. As well as

it is almost unavoidable for patients to come across falsehoods, it is also hard to avoid cognitive biases while doing research. Here comes the example of primacy effect and anchoring and adjustment heuristic. Information read as the first ones can strongly determine patients' opinions. Some respondents claim to ignore medical recommendations given by specialists even if their self-diagnosis beliefs were verified as wrong. However, there is undeniably no reason for criticising patients for their thirst for knowledge. This is no time to pretend that technical development does not exist [10]. This is time for proper health education, gathering information from appropriate sources, and considering patients and technology as partners to achieve common goals. Unfortunately, there is also no time for real discussion during the majority of medical appointments. In this way, we come back to the problem of an insufficient healthcare system.

Conclusions

Our results suggest that healthcare professional workers and medical students were more familiar with adequate knowledge about the sources of information and risk factors for self-medication. The large body of evidence concludes a significant lack of knowledge between the health sector workers and other members of society. Future studies are needed to increase people's awareness of this matter. Nowadays, HCPs should improve the educational programs of teaching patients about problems that wrong sources of information and treatment may cause without consulting a doctor. In the present situation, it is also crucial for public health to educate patients about the importance of vaccinating and encourage them to take the vaccine against the SARS-CoV2 virus causing COVID-19.

References

1. Gumiński M., Huet M., Jacykowska M., Juszczak K., Kwiatkowska M., Mordan P., Orczykowska M. Information society in Poland Results of statistical surveys in the years 2015–2019. https://stat.gov.pl/en/topics/science-and-technology/information-society/information-society-in-poland-results-of-statistical-surveys-in-the-years-20152019,1, 6. html (cited 16.07.2021).
2. Liobikienė G., Bernatonienė J.: The determinants of access to information on the Internet and knowledge of health-related topics in European countries. Health Policy,

2018, 122(12), 1348-1355.

3. Nordin I.: Expert and non-expert knowledge in medical practice. Medicine, health care, and philosophy, 2000, 3(3), 297-304.
4. Gao Z., Ying S., Liu J., Zhang H., Li J., Ma C.: A cross-sectional study: Comparing the attitude and knowledge of medical and non-medical students toward 2019 novel coronavirus. Elsevier Public Health Emergency Collection, 2020, 13(10), 1419-1423.
5. Peters D., Garg A., Bloom G., Walker D., Brieger W., Rahman M.: Poverty and access to health care in developing countries. The New York Academy of Sciences, 2008, 1136(1), 161-71.
6. Strasser R., Kam S., Regalado S: Rural Health Care Access and Policy in Developing Countries. Annual Review of Public Health, 2016, 37, 395-412.
7. Rather I., Kim B., Bajpai V., Park Y.: Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. Saudi Journal of Biology Sciences, 2017, 24(4), 808-812.
8. Abdel-Tawab M., Zettl H., Schubert-Zsilavecz M.: Nonsteroidal anti-inflammatory drugs: a critical review on current concepts applied to reduce gastrointestinal toxicity Current Medicinal Chemistry, 2009, 16(16), 2042-63.
9. Vosoughi S., Roy D., Aral S.: The spread of true and false news online. https:// science.sciencemag.org/content/359/6380/1146 (cited 27.07.2021)
10. Calixte, R., Rivera, A., Oridota, O., Beauchamp, W., Camacho-Rivera, M.: Social and Demographic Patterns of Health-Related Internet Use Among Adults in the United States: A Secondary Data Analysis of the Health Information National Trends Survey. International Journal of Environmental Research and Public Health, 2020, 17(18), 6856.

Artificial Intelligence in surgery – selected examples of use and potential future

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Abbreviation list

- AI – artificial intelligence ML – machine learning DL – deep learning
- AL – anastomosis leakage
- AUC – area under the ROC Curve ICU – intensive care unit
- AUROC – area under receiver operating characteristic curve MLP – Multilayer Perception
- BoW – bag-of-words
- ECG – electrocardiogram; electrocardiogram
- FDA – Food and Drug Administration EMA – European Medicines Agency
- MAP – mean arterial pressure RAS – robotic-assisted surgery ANN – Artificial Neural Network
- NLP – natural language processing
- PCNL – percutaneous nephrolithotomy DNN – Deep Neural Network
- RF – Random Forest ET – Extra Trees
- EU – European Union
- COVID-19 – Coronavirus disease 2019

Introduction

The concept of artificial intelligence is widely known today because the spectrum of its

applications - actual and potential - is extremely broad. It is present in various fields of science, both medical and non-medical. It is a source of inspiration for literature and film, mainly in the genre of science fiction. Before the term "artificial intelligence" was first introduced into the language, fantasies about it accompanied philosophers and writers decades or even centuries earlier.

Historical overview

Even Homer, in "The Iliad and The Odyssey", mentioned several times inventions that could work and move independently. "Book XVIII" contains a description of the forge of Hephaestus, in which individual machines work automatically. For example, these include bellows, which work once and then stop, depending on how the master commands them and what the need is. The implication is that not only are they obedient, but they can also make decisions on their own. In another fragment, Homer mentions mobile tripods constructed by Hephaestus. When finished, they will serve as useful tools for the gods [1]. A prototype machine that fits into today's definition of a robot was developed later—the third part of L. Frank Baum's Oz series, 1907's Ozma of Oz, features the mechanical man Tik-tok, who "*Thinks, Speaks, Acts, and Does Everything but Live*" [2,3]. Both Homer's and Baum's work, as well as various other cultural texts, may have inspired many explorers because they suggested the possibility of using the artificial mind as a tool.

Term "artificial intelligence"

Although visions of such technologies, which today are called artificial intelligence, were around centuries ago, it must have passed many years before the term was officially introduced. This was done by John McCarthy at the 1956 Dartmouth Conference [4,5]. Since then, AI has stood for the ability of a machine to simulate intelligence [6].

Uses of artificial intelligence

With the development of technology, AI has evolved from a visionary's idea into a tool that is widely used in both medical and non-medical fields. Currently used techniques allow computers to analyze both - structured and unstructured data. In the first case, two methods are used: machine learning (ML) and deep learning (DL). They can only operate on structured data. On the other hand, the natural language processing (NLP) technique to analyze information

does not require it to be defined in advance by a human [7]. Therefore, it is not a problem for artificial intelligence to scan many different types and forms of available information. With the accessibility of a variety of methods, it is possible to use machines to interpret a very broad spectrum of data.

AI is widely used to construct simulators of various strategic games, such as chess [8] or poker [9]. By using machine-learning techniques, it is possible to create a virtual opponent that can predict the player's moves, plan and choose the most advantageous plays. AI has also found application in computer games, where the system is supposed to interact with the player at a level as close to human as possible [10]. A promising direction of development is to introduce more and more uses of artificial intelligence techniques into the motor field. Currently, automakers are offering vehicles with so-called virtual assistants. Some companies, like Honda, want to go a step further by constructing self-driving cars [11]. Although they are not available on the market for now, it is possible that in the future, they will become an everyday reality.

Artificial intelligence techniques are now common in every field of medicine. In dermatology, AI is used in diagnostics to help clinicians differentiate skin diseases by analyzing skin image databases. This is how, inter alia, the Chinese platform AIDERMA or the mobile application SkinVision [12] work. Radiological imaging uses techniques such as ML and DL to detect potentially dangerous lesions and then characterize them. For example, AI's analysis of microcalcifications in the breast supports mammography interpretations [13]. A study by Foo, Simon Y et at. also demonstrated the effectiveness of machines in recognizing different heartbeat patterns in ECGs. In the future, this could potentially have applications in assessing a patient's heart condition and tracking its changes [14]. These are just some of the hundreds of applications, but they confirm that for modern medicine, artificial intelligence is a highly useful, even essential tool with enormous potential for development.

The applications of artificial intelligence, both in everyday life and in specialized fields, can be listed endlessly, and an exhaustive article could be written on each of them. However, this paper focuses on the usefulness of AI in surgery, including pre-operative, intra- operative and postoperative patient care.

Pre-operative care

Artificial intelligence is particularly effective in forecasting, predicting the future, so it

is an ideal tool for the prevention of very different diseases, that is, assessing the risk of their development and detection diagnosis.

One of the possible uses of artificial intelligence in surgery is the ability to predict the effects of surgical intervention and the risk of potential complications. In this way, it supports the surgeon in making decisions about possible surgery.

Very broad use of AI in the evaluation of surgical operations (to be done) is the detection and quantitative assessment of various biomarkers concentrations. An example of the use of this approach is a study using machine-learning-derived analysis to find a trait that predicts chronic postoperative pain. The authors used a cold pain test by placing the hand in cold water (approximately 4*C) and rating the pain on a numerical rating pain scale. Using AI- assisted data analysis, parameters were determined to exclude patients with persistent postoperative pain with over 94% accuracy [15].

J. K. Scheer et al. created a model to predict major complications (intraoperative and postoperative) in adult spinal deformity surgery. It is based on 45 surgical variables, radiological parameters and demographic characteristics. The AI achieved an overall accuracy of 87.6% with an AUROC curve (area under receiver operating characteristic curve) of 0.89. There were 20 variables with the highest importance in the model, which mainly included age, leg pain, Oswestry Disability Index, and a number of decompression levels [16].

A pilot program conducted on the global ASSIST registry ("collecting information related to various techniques of mechanical thrombectomy in large vessels" [17]) created an artificial intelligence-based model predicting the risk of death in surgery for congenital heart defects [18]. More than one million children are born with heart defects each year worldwide, so it is a socially important disease worldwide [18].

This study tried to use different AI models such as Multilayer Perception (MLP), Random Forest (RF), Extra Trees (ET) and others. RF proved to be the best option with an AUC=0.902 [18].

A number of characteristics affecting neonatal survival during the mentioned surgeries were listed, including previous ICU admissions, body height, body weight, blood saturation and pulmonary atresia [18].

Intra-operative care

Artificial intelligence has also found applications in assisting the surgical team during

operations. From algorithms that can predict emergencies based on patient parameters, to autonomous robots that can independently perform certain tasks within the surgeon's competence. Currently, a much more developed area are algorithms designed to assist surgeons or anesthetists in making decisions during operations. This is understandable not only because of the difficulty of creating machines capable of imitating the precise movements of the surgeon, but also because in order to create a machine capable of independent operations, we must first teach the computer to make decisions independently and accurately. So a path where technologies are first developed to teach artificial intelligence to think for itself and advise the surgical team is most natural. A machine must first learn to make decisions on its own in order to be able to operate independently afterward.

Correct decision-making during surgery is crucial to its final outcome. For this reason, many researchers have focused their attention on the use of AI to help make these decisions. Based on the scientific articles we reviewed, we have distinguished two main directions for artificial intelligence in intraoperative counseling: aiding in cancer detection/differentiation and more generally, helping to decide what to do in other non-oncological cases. There are already many algorithms that, based on the data provided, are able to detect where a tumor is in the human body, determine whether it is healthy or cancerous tissue, and even determine the type of cancer or its nature [19].

Determining the location of a tumor can take place as a result of, for example, intraoperative analysis of the distribution of contrast agent or with the help of hyperspectral imaging. The distribution of contrast medium is helpful in that it will be most abundant where there is a more vascularized area than surrounding areas, which may suggest the existence of a tumor. Using this method as a source of information, the two best algorithms were able to detect glioblastoma in patients with an accuracy of 0.71 and 0.9507. Interestingly, the first algorithm did not have a ready-made database from which to draw conclusions, but it learned during surgery from the tissue of the operated patient. The surgeon had to mark 2 areas with cancer and two without on the patient's body, and on this basis, the program learned to recognize new tumors in the same patient. The learning process itself took about 3 seconds, so it could be used during surgical practice.

The next group of algorithms that assist the surgical team in decision-making is those that provide information on the characteristics of the tissue involved. Allison, 2020 lists a number of papers, which handled different algorithms, that depending on the work, were able to distinguish pathological colorectal polyps from benign ones with a high success rate (94.2%),

to distinguish meningiomas from glioblastomas using probe-based confocal laser endomicroscopy with a success rate of up to 99.49%, or to distinguish normal lymph nodes from metastatic lesions using other methods and to distinguish glioblastoma from normal tissue [19].

Also, Martini [2020] in his work, demonstrated the existence of a neural network that was able, on the basis of sections taken from the patient and analyzed by Stimulated Raman spectroscopy, to distinguish tumor tissue from normal brain tissue. Moreover, she achieved this result faster (examination time: 2-3 minutes) and with higher efficiency (94.6%) than pathologists (93.9%) who used the standard cryosection slide preparation technique for diagnosis [20]. The above achievements of artificial intelligence can be an invaluable aid, for example, in deciding whether to perform a biopsy or in determining the extent of pathological tissue excision. This is a great help not only due to higher efficiency and lower time consumption for diagnostics by physicians but also because the quality of pathologists and samples taken does not influence the correctness of the diagnosis.

Another type of algorithms we have highlighted are those not related to cancer. Lundberg presented an algorithm based on machine learning that was able to predict in a patient under general anesthesia the probability of being in a hypoxic state before surgery and to detect the upcoming hypoxic state every minute of the surgery 5 minutes before it occurs. AI was able to predict these health-threatening conditions significantly more effectively than anesthetists in both of the cases ($p<0.0001$). In addition, AI provides the reason for its predictions, which could enable anesthetists to intervene more effectively and prevent hypoxic conditions. A positive effect on the prediction of hypoxia by anesthesiologists was also demonstrated when they relied not only on their own experience but also on the clues provided to them by AI. They achieved significantly better results with AI than without it
($p<0.0001$). Furthermore, it has been shown that by increasing the AI learning database, its effectiveness in detecting hypoxic conditions is also increased. This effectiveness could probably also be increased by decreasing the time interval before the hypoxia event [21].

An algorithm that detects states of hypotension in a patient under general anesthesia provides a similar aid to anesthetists in predicting states that are dangerous to the patient's health. This algorithm was programmed to recognize a low-pressure state from MAP values <65mm Hg and normal pressure from values >75mm Hg. It was designed to calculate the probability of hypotension in patients 5, 10, and 15 minutes before the event and to return point values to clinicians where prophylactic treatment against low blood pressure was recommended

from certain values. This algorithm has been tested in practice. 2 retrospective trials have shown the high effectiveness of the above algorithm in predicting hypotensive states. There were also two randomized controlled trials to compare the time spent in hypotension in patients undergoing standard medical care and in those where doctors suggested prompts from AI. In both studies, patients of physicians, who were healing the patients based on the AI warnings about the risk of hypotension spent significantly less time in a hypotensive state than when physicians used standard procedures alone ($p<0.001$). In these studies, physicians intervened in response to 77.8% and 81% of alerts from AI. One of these studies showed that AI does not affect the number of drugs and fluids used to control hypotension but the frequency and doses at which they are administered. This means that the less time spent in hypotension was not due to an excess of drugs used, but to the accuracy of the choice of their use and amount, to which AI contributed [22].

AI has also found application in eye surgery. Tian et al., in his work on the use of AI during cataract surgery, presented an algorithm capable of not only recognizing the eye or tracking surgical instruments with high efficiency but also able to recognize cataracts with 99.2% efficiency and was able to determine lens hardness with 96.3% efficiency [23], which is known to be closely related to the degree of cataract severity [24]. The above achievement is a good start for the development of autonomic cataract surgery of the eye. The algorithm recognizing the degree of cataract, after some further improvements, will also be able to determine the amount of ultrasonic energy needed to perform phacoemulsification. In this case, the doctor's role would only be to manually perform the maneuver, and all the values would be determined and selected for him by artificial intelligence. Thus, this creates the possibility of creating a machine capable of assisting surgeons to a large extent [23].

Another example of AI assisting in intraoperative counseling is in helping to recognize anatomical structures. In the laparoscopic surgery setting, it is difficult to recognize some structures of similar appearance that could be recognized by touch in open surgery. This is where neural networks can help, learning from thousands of surgical images how to recognize given structures based on appearance alone. Harangi et al. presented work in which, by learning a neural network, a system was created capable of distinguishing with 94.2% efficiency between the uterine artery and ureter, i.e., two structures visually very similar to each other [25]. Solutions based on this principle could help reduce misdiagnoses and, therefore postoperative complications.

However, the help of artificial intelligence during surgery may manifest itself in more

than just advising on decisions. Miehle 2017 in her work, presented the concept of creating a program that would help surgeons in a completely different way. It would be a speech-controlled program (there are already advanced programs that understand human speech such as Siri or Alexa), which, on the surgeon's instructions, could change the lighting of the room, the positioning of the operating table, display patient data, or, for example, save the doctor's favorite settings and prepare the operating room at the surgeon's discretion. This would provide an irresistible aid and comfort in conditions where the surgeon must remain sterile. A voice control function in these conditions would be very helpful [26].

Although machines capable of autonomous surgery are, for the time being, a distant future and a machine capable of performing autonomous surgery do not yet exist, research in this area is already underway [27]. The first step to create such machines is to define standard algorithms for the procedure and to detail the steps in treatment. A particularly important aspect is the standardization and creation of guidelines for performing surgical suturing, which is a regular part of a surgeon's work. Jackson and Cavusoglu have created a broad description of the behavior of the ½ circle needle during suturing on the basis of an extensive mathematical analysis of the needle movement trajectory and the experience of surgeons [28]. From this, it is possible to predict how the needle will behave or to what depth the needle should be inserted, knowing the entry and exit point. Another equally important aspect is the behavior of the tissue during needle insertion and the calculation of the optimal way to insert the needle so that this deformation is as small as possible, which has also already been described [27]. All of this is an important start to creating a program able to perform effective suturing during surgery on its own. There are also robots capable of autonomously performing surgical knots based on iterative learning from human demonstrations. Moreover, they are capable of tying these knots faster than humans (using laparoscopic tools) and of performing set movements with laparoscopic tools more precisely than humans [29]. There are also robots that are able to place sutures more precisely and regularly than a human, but only in experimental conditions. The STAR robot, when compared to the performance of surgeons placing sutures manually, is able to place sutures with more regular spacing between sutures and by performing the same amount of needle repositioning (the less, the better, as this prevents unnecessary tissue damage). Moreover, this robot achieves a shorter time, performs fewer needle repositions, and maintains more regular spacing than surgeons using laparoscopy and RAS with da Vinci Surgical System [30,31]. Although these robots are not based on artificial intelligence but only on algorithmics, we decided to mention it because it will certainly be the key to the development of fully automated machines capable of performing surgeries on their own in the future.

Postoperative care

When considering the roles of artificial intelligence in surgery, its use after the surgical procedure should also be considered. Improvements in this area will impact the speed of patient recovery, to a significant degree. This publication highlights the most prosperous applications of AI in postoperative care in the areas of prediction, monitoring, and telemedicine.

The term "prediction" covers a wide range of AI applications. For proper patient care, the ability to predict the outcome of a procedure and its potential complications and other risks is critical. This allows for the rapid implementation of additional treatment and the selection of the most effective management methods that are individualized for each case. There are an extremely large number of variables that significantly determine the outcome of surgery, so their analysis is an effective method of prediction. However, the vast amount of data available is impossible for the clinician to analyze, so machines find their role in this area.

Machine learning techniques were used by Aminsharifi A. *et al.* to create an Artificial Neural Network (ANN) model that can effectively predict the outcome of percutaneous nephrolithotomy (PCNL). This is a procedure used to treat urinary tract stones. The constructed model showed specificity and sensitivity ranging between 81.0% and 98.2%, confirming its potential usefulness in postoperative patient care. A variety of data were used, both preoperative, intraoperative, and postoperative, which certainly had a positive impact on the accuracy of the algorithm. Modern diagnostic techniques allow physicians to obtain vast amounts of information about a patient and his or her condition. In contrast, artificial intelligence has virtually no limitations in its interpretation. Therefore, the development of analytical methods drives the development of AI techniques and *vice versa*. In the case of PCNL, the successful prediction of the outcome of surgery can significantly reduce the time of hospitalization of the patient, thanks to the immediate implementation of additional procedures. This entails many benefits. For example, the patient will be able to leave the hospital and return to normal life sooner. For the facility, this means reduced costs and also a decrease in the use of human resources [32].

Hopkins B. et. al. also looked at the issue of predicting postoperative complications. In their work, they attempted to construct a system that would effectively predict the occurrence of infection after posterior spinal fusion surgery. In this case, deep learning techniques were applied and a Deep Neural Network (DNN) model was built. To evaluate the performance of the DNN system, the positive and negative predictive values were calculated, which were

92.56% and 98.45%, respectively. This demonstrates the effectiveness of the applied AI technique in predicting the occurrence of postoperative infection. Moreover, the described model allowed distinguishing the factors that most increase or reduce the risk of infection. With this type of data, it is possible to quickly identify a group of patients particularly vulnerable to complications after surgery and provide them with special care during recovery. In addition, knowing the impact of certain modifiable characteristics on the risk of the described complication, clinicians will be able to reduce it. For example, according to the constructed algorithm, the use of steroid drugs more than nonsteroidal immunosuppression increases the risk of postoperative infection. Therefore, this fact may be considered while customizing the proper pharmacotherapy for the patient. This observation offers hope that AI techniques can be used to maximally reduce the risk factors for any postoperative complications [33].

A technique other than machine learning was used by Soguero-Ruiz C. *et al.* They built a bag-of-words (BoW) model to predict the occurrence of anastomosis leakage (AL). This is a complication of elective colorectal cancer surgery, affecting up to 15% of patients, which in the worst case can end in death. The essence of the action of the system described above is to highlight the words or phrases that appear most frequently in the records of patients who have experienced a particular complication. The model trained in this way will be able, on the basis of appearing in clinical records words, more or less related to AL, to determine the risk of its occurrence [34]. Typically, the first clinical signs of AL do not appear until at least five days after surgery [35]. Thus, a relatively long period of time must pass before a physician can diagnose the complication and, thus, before he can implement the treatment. Since response time plays a crucial role in such a serious complication, early detection has a significant impact on patient prognosis. The use of artificial intelligence to predict anastomosis leakage makes it possible to isolate vulnerable patients and to show special care and accuracy when monitoring their condition after surgery. The model described by BoW demonstrated sensitivity and specificity of 100% and 72%, respectively, so its effectiveness in predicting potential postoperative complications can be admitted [34].

Surgery procedures may be very demanding on the body, and it happens that the patient's condition after surgery becomes dangerously destabilized. Sometimes this is an immediate threat to the patient's life; other times it may result in a failure of the surgery, such as rejection of the transplant. Therefore, it is very important to constantly monitor the patient's condition after surgery, and any error or delay may lead to negative consequences. Since evaluation on the part of the clinician is subjective, Kiranantawat K. *et al.*, for monitoring free flap tissue

perfusion, decided to involve artificial intelligence as support. They created a cell phone application for this purpose called SilpaRamanitor. After photographing the skin of the transplanted tissue, the software is able to detect the obstruction in a vessel leading to disturbance of blood flow in the free flap. Moreover, the type and degree of the pathology can be assessed. At the validation stage, the specificity and sensitivity of the program were determined and were 98% and 94%, respectively. The effectiveness of the application was then confirmed in a clinical test conducted on a woman after breast reconstruction with the rectus abdominis muscle. The study showed that artificial intelligence is able to detect perfusion abnormalities faster than it begins to give clinical symptoms. Doctors are able to see changes in the color of the skin of the tissue in which the obstruction of a blood vessel has occurred, but it turned out that the application based on machine-learning technique can do this faster. Furthermore, any changes in tissue blood supply are particularly difficult to see in patients with darker skin color. In contrast, this is not an obstacle for the application. This proves that in monitoring a patient's condition after surgery, an AI-based model can be a useful tool to speed up diagnosis and management in case of postoperative complications [36].

Postoperative care does not end after the patient leaves the medical facility. His or her health status should be monitored even after hospitalization ends. As of today, the most time-saving way to consult a patient is a phone call. Bian Y. et al. found an application for artificial intelligence in this aspect, to maximize telephone follow-up after orthopedic surgery. For this purpose, an AI-based system was constructed that automatically called patients and collected feedback from them. The effectiveness of AI was then compared t o that of manually made phone calls. The biggest noted benefit of using AI is certainly the time savings, as the described method does not require any human involvement [37].

Thus, the time required for AI to perform a follow-up is 0 hours. A common problem that hospitals face is deficiency of human resources. When there is a shortage of doctors and nurses to work on site, it is difficult to find a person who can additionally take up phone calls with postoperative patients [37].

Therefore, this is where artificial intelligence can find its application and has the potential to develop. The information collected by the system is entered into databases, so clinicians always have access to it and can use it when there is time and when it is needed. Admittedly, the method described is not routinely used in postoperative care at this point, but it has demonstrated high effectiveness, and there is a chance for it to be gradually introduced into medicine [37].

Surgeons' role in ai development

Machine learning is beginning to play a large role in more and more areas of human life including medicine and surgery.

Humans are not able to process and remember as much data as computers, so it is natural that with the introduction of algorithms capable of interpreting such large amounts of data, the computer will become an increasingly important and necessary member of the operating team.

Many researchers developing the aforementioned programs or machines are announcing further work to improve these projects, while others are trying to discover new ones. However, this does not mean that the computer will completely replace man. It should be remembered that it is still the man who is the reference on the basis of which all programs and AI in medicine learn. It is the doctor's diagnosis that is referred to as the zero points, the absolute truth on the basis of which computers interpret the given data. It should also be emphasized here how important the role of doctors and surgeons is in the development of AI. Without their results, a computer would be deprived of a database on which it could learn. Therefore, the responsibility for the development of artificial intelligence technology does not rest only on the shoulders of computer scientists but also to a great extent on doctors.

It is difficult to predict the future of surgery, yet what is certain is that machines and artificial intelligence will play an increasingly important role in it.

Limitations

Limitations to the development and use of AI can be divided into three main categories: technical, ethical, and legal.

Technical limitations are caused by always insufficient data. In other words, there is never enough data that could not improve the quality of the model is created. For this reason, some "tricks" are used, which can multiply the amount of initial material/size of the initial dataset for learning [38]. Length of teaching also affects the final effect on the effectiveness of AI. Teaching too long (and other reasons) can also be detrimental ("overfitting"), likewise "underfitting" the model by learning too short ("underfitting") [39].

One might also suspect that current methods for creating and developing AI methods are not implicitly optimal. It is often necessary to use statistical methods to verify AI activities [40].

Another problem is that in some types of AI (e.g. ANN) there are so-called 'hidden layers', through which it is unknown how such a system of 'neurons' works. This situation in ANNs is referred to as a 'black box' because the system learns on its own, and there is no formal theory to increase the reliability of the model [41]. Furthermore, the conclusions drawn by the model are sometimes difficult to interpret [42].

Artificial intelligence can largely be described as very specialized software. By this characteristic, it is susceptible to hacking or intentional input of incorrect data. Such situations should be taken into account both in software development and in legislation and procedures for regular testing and evaluation of system functions. Ensuring the highest levels of security is extremely important, as AI takes care of human life and health and is potentially extremely vulnerable to attacks by hacking or terrorist groups [43].

Bringing AI software (and possible mechanisms for its use) to the health market is costly and must proceed through procedures before the medical agencies that authorize the technology (e.g., FDA, EMA, Office for Registration of Medicinal Products). The expenses incurred globally by 2024 could reach $110 billion [44].

In addition, the digital revolution, of which the use of AI is a large part, certainly requires social change, which can be very challenging [45].

Ethical constraints are also an extremely broad issue - in 2019 the Institute for Ethics in Artificial Intelligence in Munich, Germany, was established. In this work, we will consider the division of ethical problems into those that are potential and those that we already face.

Potential constraints include, for example, the gaining of consciousness by AI and the implications of this - should AI have the right to self-determination? As AI becomes more autonomous, it may become independent in ways that are not controlled by humans, potentially posing a threat.

As the use of AI increases, so will its impact on our lives. This means that entire societies may become dependent on its services and increased efficiency, causing potential social problems. Also, it is important to secure against its potential failure or error, so they must be taken into account and legally regulated, as further described below.

We also now already have ethical problems with AI, which relate to areas such as downsizing in jobs with repetitive activities, or the unethical use of AI, for hacking, terrorism, or spying, for example.

One reason AI is being introduced is to reduce the possibility of a surgeon making a mistake, but no system is 100% infallible. It is possible to predict that AI will make a mistake,

so one should prepare for such a situation: should the AI performing the surgery then activate a safety procedure, which may involve focusing on the patient's basic vital functions or handing over control to the surgeon? In the case of postoperative complications and possible claims by the injured, legal standards should be established: who is responsible for failures, in what cases, and to what extent. Currently, the law does not regulate this issue, but it is proposed that each situation should be evaluated individually [46].

In summary, the legal regulations should include the principles of allowing AI for use in medicine (including surgery), including the identification of the institution authorized to approve its use and determine its parameters, the principles of applicability, as well as persons responsible for its use, and monitoring of abnormalities in its operation (in the case of negative performance).

Legal regulations should also address the responsibility for inappropriate use of AI by medical personnel, inappropriate source of purchase (compliance with the requirements for approval for the use), appropriate service, principles of physician intervention in the event of AI malfunction - as well as notification of intervention based on the best medical knowledge.

Currently, in Polish law, there is no defined concept of artificial intelligence, although it appears several times [47,48].

On the other hand, the European Parliament is working on a package of legislation on opportunities and threats related to the development of artificial intelligence [49], but already on February 19, 2020. European Commission published "White Paper on Artificial Intelligence A European approach to excellence and trust" [50]. It describes the EU's approach to AI development. Although it is not a legal act, it sets the direction for future changes in law. Also in Poland, the importance of AI issues is beginning to be recognized. The "Policy for the development of artificial intelligence in Poland from 2020" has been established [51].

There are concepts of creating a third legal personality - an electronic person (in addition to a natural person and a legal person). In connection with this concept, further doubts arise about the responsibility for potential errors, especially in cases where they would be caused by the actions of third parties (in particular, hackers) [52].

A major technical-ethical problem may become that AI often learns by generalizing. This leads to the fact that if the data is homogeneous with respect to some trait (e.g., race or gender), AI will be better at predicting those traits that it has had the opportunity to learn better. Such an error, associated with the heterogeneity of the input data in terms of, for example, people's race, is called bias (in this case: race bias). At the same time, artificial intelligence can

also potentially reduce racism and other types of discrimination (e.g., based on gender) [53]. In general, it can be said that data can be tendentious, and therefore, the program will also learn to interpret it in a biased way.

It is now proposed that to mitigate any risks associated with expanding the role of AI in our lives, we should apply the four basic principles of its development: transparency, explainability, inclusiveness, and alignment [54] and universal basic principles, similar to Isaac Asimov's laws of robots.

Opportunities

Introduction of artificial intelligence to medicine, but also to other areas of life has the potential to become a revolution on par with the industrial revolution or the introduction of the Internet. It is expected to significantly increase productivity, reduce adverse effects and consequently improve patient care, especially prevention. Artificial intelligence is expected to be a key element related to the EU recovery plan after COVID-19 [49]. The indirect economic impact of artificial intelligence through work automation could account for up to €12 000 billion per year [49] and account for $100 billion per year in savings in US health- care system [55].

Summary

Artificial intelligence will play an increasingly important role in surgery and the whole of medicine. Its use may manifest itself in predicting diseases, risk of complications, and chances of completing procedures successfully, and even performing surgical procedures such as suturing or excision on its own. All this will improve the availability and effectiveness of surgical care for the patient, allow more optimal management of resources and increase the therapeutic success rate. Despite the great hopes placed on artificial intelligence, there are also a number of concerns about radically changing the situation in the world. It is precisely because of the anxiety and the unknown potential consequences of the introduction of AI; there are regulatory restrictions that will have to be imposed on its development.

In the development of AI in medical fields and especially in surgery, it will be necessary to have specialists in artificial intelligence, data-science but also high-class doctors, surgeons on whose experience the programs can develop.

References

1. Vasileiadou S. and Kalligeropoulos D.: Myth, theory and technology of automatic control in ancient Greece. Control Conference (ECC), 2007, 1-2.
2. Buchanan B.G.: A (Very) Brief History of Artificial Intelligence, 2005, 1.
3. Baum L.F.: Ozma of Oz. Available: https://thevirtuallibrary.org, 1907, 30.
4. Mintz Y. and Brodie R.: Introduction to artificial intelligence in medicine. Minimally Invasive Therapy & Allied Technologies, 2019, 28(2), 73–81.
5. Haenlein M. and Kaplan A.: A brief history of artificial intelligence: On the past, present, and future of artificial intelligence. California Management Review, 2019, 61(4), 5–14.
6. McCarthy J., Minsky M.L., Rochester N., and Shannon C.E.: A Proposal for the Dartmouth Summer Research Project on Artificial Intelligence, 2006, http://jmc .stanford.edu/articles/ dartmouth/dartmouth.pdf (cited 29.07.2021).
7. Kung W.M. and Lin M.S.: CT-Based Quantitative Analysis for Pathological Features Associated With Postoperative Recurrence and Potential Application Upon Artificial Intelligence: A Narrative Review With a Focus on Chronic Subdural Hematomas. Molecular Imaging, 2020, 19, 1536012120914773.
8. Villa A.E.P., Masulli P., Pons Rivero A.J., Eds.: Artificial Neural Networks and Machine Learning – ICANN 2016. Cham: Springer International Publishing, 2016, 9887, 1-9.
9. Mcnally P., Rafii Z.: Opponent modeling in poker using machinelearning techniques, https://users.cs.northwestern.edu/~ddowney/courses/349_Fall2008/projects/poker/Poker.pdf (cited: 29.07.2021).
10. Laird J.E. and Van Lent M.: Human-Level AI's Killer Application. Interactive Computer Games AI Magazine, 2001, 22(2), 1-2.
11. Rak J.: Polish Association of Telecommunication Engineers,Institute of Electrical and Electronics Engineers, and IEEE Poland Section, Proceedings of 2017 15th International Conference on ITS Telecommunications (ITST), 2017, May 29-31, 1-5.
12. Li C.X., Shen C.B., Xue K., Shen X., Jing Y., Wang Z. Y., Xu F., Meng R.S., Yu J.B. and Cui Y.: Artificial intelligence in dermatology: Past, present, and future. Chinese Medical Journal, 2019, 132(17), 2017–2020.
13. Hosny A., Parmar C., Quackenbush J., Schwartz L.H., Aerts H.J.W.L.: Artificial intelligence in radiology. Nature Reviews Cancer, 2018, 18(8), 500–510.

14. Foo S.Y., Stuart G., Harvey B., Meyer-Baese A.: Neural network-based EKG pattern recognition. Engineering Applications of Artificial Intelligence, 2002, 15(3-4), 253-260.
15. Lötsch J., Ultsch A., Kalso E.: Prediction of persistent post-surgery pain by preoperative cold pain sensitivity: Biomarker development with machine-learning- derived analysis, British Journal of Anaesthesia, 2017, 119(4), 821–829.
16. Scheer J.K., Smith J.S., Schwab F., Lafage V., Shaffrey C.I., Bess S., Daniels A.H., Hart R.A., Protopsaltis T S., Mundis G.M. Jr., Sciubba D.M., Ailon T., Burton D.C., Klineberg E., Ames C.P., the International Spine Study Group: Development of a preoperative predictive model for major complications following adult spinal deformity surgery. Journal of Neurosurgery: Spine, 2017, 26(6), 736–743,
17. Clinical Research Trials. https://www.mclaren.org/main/clinical-research-trials/156 (cited 14.05. 2021).
18. Chang J. Jr., Binuesa F., Caneo L. F., Luiza A., Turquetto R., Arita E.C.T. C., Barbosa A. C., da Silva Fernandes A.M., Trindade E.M., Jatene F.B., Dossou P.E., Jatene M.B.: Improving preoperative risk-of-death prediction in surgery congenital heart defects using artificial intelligence model: A pilot study. PLoS One, 2020, 15(9), 1–21,
19. Navarrete-Welton A.J. and Hashimoto D.A.: Current applications of artificial intelligence for intraoperative decision support in surgery. Frontiers in Medicine, 2020, 14(4), 369–381.
20. Martini M.L. and Oermann E.K.: Intraoperative brain tumour identification with deep learning. Nature Reviews Clinical Oncology, 2020, 17(4), 200–201.
21. Lundberg S.M., Nair B, Vavilala M.S., Horibe M., Eisses M.J., Adams T., Liston D.E., King-Wai Low D., Newman S., Kim J., Lee S.: Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. Nature Biomedical Engineering, 2018, 2(10), 749–760.
22. Van der Ven W.H., Veelo D.P., Wijnberge M., Van der Ster B.J.P., Vlaar A.P. J., Geerts B. F.: One of the first validations of an artificial intelligence algorithm for clinical use: The impact on intraoperative hypotension prediction and clinical decision-making. Surgery. (United States), 2020, 169(6), 1300-1303.
23. Tian S., Yin X.C., Bin Wang Z., Zhou F., and Hao H.W.: A Video-Based Intelligent Recognition and Decision System for the Phacoemulsification Cataract Surgery. Computational and Mathematical Methods in Medicine, 2015, 2015, 202934.

24. Heyworth P., Thompson G.M. and Mc Guigan S.: The relationship between clinical classification of cataract and lens hardness. Eye, 1993, 7(6), 726–730.
25. Harangi B., Hajdu A., Lampe R., and Torok P.: Recognizing Ureter and Uterine Artery in Endoscopic Images Using a Convolutional Neural Network, 2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS), 2017, 726–727.
26. Miehle J., Ostler D., Gerstenlauer N., Minker W.: The next step: Intelligent digital assistance for clinical operating rooms. Innovative Surgical Sciences, 2020, 2(3), 159–161.
27. Attanasio A., Scaglioni B., De Momi E., Fiorini P., Valdastri P.: Autonomy in Surgical Robotics. Annual Review of Control, Robotics, and Autonomous Systems, 2021, 4(1), 1–29.
28. Jackson R. C. and Cavusoglu M. C.: Needle path planning for autonomous robotic surgical suturing. Proc. – IEEE- International Conference on Robotics and Automation, 2013, 1669–1675.
29. Van Den Berg J., Miller S., Duckworth D., Hu H., Wan A., Fu X., Goldberg K., Abbeel P.: Superhuman performance of surgical tasks by robots using iterative learning from human-guided demonstrations. Proc. - IEEE - International Conference on Robotics and Automation, 2010, 2074–2081.
30. Shademan A., Decker R.S., Opfermann J.D., Leonard S., Krieger A., Kim P.C.W.: Supervised autonomous robotic soft tissue surgery. Science Translational Medicine, 2016, 8(337), 337ra64.
31. Saeidi H., Le H.N.D., Opfermann J.D., Leonard S., Kim A., Hsieh M.H., Kang J.U., Krieger A.: Autonomous laparoscopic robotic suturing with a novel actuated suturing tool and 3d endoscope. Proc. - IEEE - International Conference on Robotics and Automation, 2019, 1541–1547.
32. Aminsharifi A., Irani D., Pooyesh S., Paris H., Dehghani S., Yousofi K., Fazel E., Zibaie F.: Artificial Neural Network System to Predict the Postoperative Outcome of Percutaneous Nephrolithotomy. Journal of Endourology, 2017, 31(5), 461–467.
33. Hopkins B.S., Mazmudar A., Driscoll C., Goergen J., Kelsten M., Shlobin N.A., Kesavabhotla K., Smith Z.A. and Dahdaleh N.S.: Using artificial intelligence (AI) to predict postoperative surgicalsite infection: A retrospective cohort of 4046 posterior spinal fusions. Clinical Neurology and Neurosurgery, 2020, 192, 1-4.

34. Soguero-Ruiz C., Hindberg K., Rojo-Álvarez J. L., Skrøvset S.O., Godtliebsen F., Revhaug A., Lindsetmo R.O., Augestad K.M. and Jenssen R.: Support Vector Feature Selection for Early Detection of Anastomosis Leakage from Bag-of-Words in Electronic Health Records, IEEE. Journal of Biomedical and Health Informatics, 2016, 20(5), 1404–1415.
35. Daams F., Luyer M., Lange J. F.: Colorectal anastomotic leakage: Aspects ofprevention, detection and treatment. World Journal of Gastroenterology, 2013, 19(15), 2293–2297.
36. Kiranantawat K., Sitpahul N., Taeprasartsit P., Constantinides J., Kruavit A., Drimuninnimit V., Punyahotra N., Chatdokmaiprai C. And Numhom S.: The first Smartphone application for microsurgery monitoring: SilpaRamanitor. Plastic and Reconstructive Surgery, 2014, 134(1), 130–139.
37. Bian Y., Xiang Y., Tong B., Feng B., Weng X.: Artificial intelligence-assisted system in postoperative follow-up of orthopedic patients: Exploratory quantitative and qualitative study. Journal of Medical Internet Research., 2020, 22(5), 1-8.
38. Rozszerzanie danych | TensorFlow Core. https://www.tensorflow.org/tutorials/images /data_augmentation (cited 14.05.2021).
39. Przebranie i podbicie | TensorFlow Core. https://www.tensorflow.org/ tutorials/keras/ overfit_and_underfit (cited 14.05.2021).
40. Marzban C.: Basic statistics and basic AI: Neural networks [in:] Artificial Intelligence Methods in the Environmental Sciences. Editors: Marzban C., Haupt S. E., Pasini A., Springer, 2009, 15–47.
41. Dosilovic F.K., Brcic M., Hlupic N.: Explainable artificial intelligence: A survey, 2018 41st Int. Conv. Inf. Commun. Technol. Electron. Microelectron. MIPRO2018 - Proc., 2018, 210–215.
42. Liyanage H., Liaw S., Jonnagaddala J., Schreiber R., Kuziemsky C., Terry A.L., de Lusignan S.: Artificial Intelligence in Primary Health Care: Perceptions, Issues,and Challenges. Yearbook of Medical Informatics, 2019, 28(1), 41–46.
43. Hartmann K., Steup C.: Hacking the AI - The Next Generation of Hijacked Systems. International Conference on Cyber Conflict, CyCon, 2020, 2020-May, 327–349,
44. 110 mld $ na sztuczną inteligencję|Platforma Przemysłu Przyszłości. https://przemysl przyszlosci.gov.pl/110-mld-na-sztuczna-inteligencje/ (cited 14.05.2021).
45. Perc M., Ozer M., Hojnik J.: Social and juristic challenges of artificial intelligence. Palgrave Communications, 2019, 5(1), 1–7.

46. Czochra M., Bar D.: The Death of the Patient as a Consequence of Using AI in Medical Technology – Crime Analysis. Studies in Law: Research Papers, 2019, 2(25), 67–82,
47. USTAWA z dnia 17 stycznia 2019 r. o Fundacji Platforma Przemysłu Przyszłości, 2019.
48. ROZPORZĄDZENIE RADY MINISTRÓW z dnia 7 czerwca 2017 r. w sprawie nadaniaNaukowej i Akademickiej Sieci Komputerowej statusu państwowego instytutu badawczego, 2017.
49. Regulacje ws. sztucznej inteligencji: oczekiwania Parlamentu | Aktualnści | Parlament Europejski. https://www.europarl.europa.eu/news/pl/headlines/society/20201015STO89417/regulacje-ws-sztucznej-inteligencji-oczekiwania-parlamentu (cited 14.05.2021).
50. Komisja Europejska, BIAŁA KSIĘGA w sprawie sztucznej inteligencji Europejskie podejście do doskonałości i zaufania. https://ec.europa.eu/info/sites/default/files/commission-white-paper-artificial-intelligence-feb2020_pl.pdf (cited 14.05.2021).
51. UCHWAŁA NR 196 RADY MINISTRÓW z dnia 28 grudnia 2020 r. w sprawie ustanowienia Polityki dla rozwoju sztucznej inteligencji w Polsce od roku 2020, 2021.
52. Kielar J.: Sztuczna inteligencja w służbie medycyny - wg prof. Zajdel-Całkowskiej potrzebne lepsze prawo. https://www.prawo.pl/zdrowie/sztuczna-inteligencja-w-sluzbie- medycyny-wg-prof-zajdel,505343.html (cited 14.05.2021).
53. Pierson E., Cutler D.M., Leskovec J., Mullainathan S., Obermeyer Z.: Analgorithmic approach to reducing unexplained pain disparities in underserved populations. Nature Medicine, 2021, 27(1), 136–140,
54. AI Ethics in 2021: Top 9 Ethical Dilemmas of AI. https://research.aimultiple.com/ai-ethics/#how-to-navigate-these-dilemmas (cited 14.05.2021).
55. How big data can revolutionize pharmaceutical R&D | McKinsey. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/how-big-data-can-revolutionize-pharmaceutical-r-and-d# (cited 14.05.2021).

Cataract in Pseudoexfoliation Syndrome

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Abbreviation list

- AGEs - Advanced Glycation End-products
- CTR – Capsular Tension Ring
- ECCE - Extracapsular Cataract Extraction
- FBLN5 gene – Fibulin-5 precursor
- IOL – Intraocular Lens
- IOP - Intraocular Pressure
- IOP – Intraocular Pressure
- LOXL1 - Lysyl Oxidase-Like 1
- OAG - Open-Angle Glaucoma
- OVD - Ophthalmic Viscosurgical Device
- PEG - Pseudoexfoliation Glaucoma
- PEX, PXF – Pseudoexfoliation syndrome
- POAG - Primary OAG
- PXM - Pseudoexfoliative material
- ROS – Reactive Oxygen Species
- SOAG - Secondary Open-Angle Glaucoma
- UBM - Ultrasound Biomicroscopy

Introduction

Pseudoexfoliation syndrome (PEX, PXF) is an elastosis – the degenerative disease that

manifests itself by an accumulation of excessive fibrillar material in the extracellular matrix. John G. Lindberg was the first to describe that illness in 1917 [1]. The exfoliative material may be present in various organs, such as the heart, lungs, vessels, gallbladder, kidneys, liver, urinary bladder, and meninges. Clinically, ocular manifestation is the most significant as well as the most conspicuous one. As concerns eye tissue, the anterior lens capsule, trabecular meshwork, ciliary body, ciliary zonule, iris, anterior hyaloid membrane, cornea, conjunctiva are the sites of accumulation [2,3]. It is acknowledged that the occurrence of PEX increases the risk of intra- and postoperative complications of cataract surgery. Taking patients referred for lens replacement surgery into account, the prevalence of coexisting PXF differs in certain populations, e.g. 40,9% Somali, 39,3% Ethiopia, 27,9% Greece, 21% Poland, 11% Turkey [4,5,6,7,8]. Notwithstanding, the risk of both mentioned disease entities increases with age.

Pathogenesis

Pathogenesis of PEX is based on abnormal and excessive cross-linking of elastic microfibrils into fibrillar exfoliative aggregates and impaired defensive functions against free radical damage [9]. Alike to the other age-related, degenerative diseases – oxidative stress and glycation are the processes of great importance in PXF pathogenesis. As a result, the correct conformation of macromolecules is impaired leading to their aggregation in the extracellular matrix. Concerning glycation, high AGEs (Advanced Glycation End-products) levels were found in patients with PEX [10]. Hence, diabetes mellitus may suggest a probability of exfoliative material formation. As regards oxidative stress, this process evolves in case of imbalance between the production of ROS (Reactive Oxygen Species) and antioxidants formation or their activity. Suggestively reduced levels of antioxidants, e.g. glutathione and ascorbic acid are noticed in patients with PEX [11]. In opposition, higher amounts of ROS were indicated [12].

Accumulated toxic free radicals damage lipids in the peroxidation process, which results in destabilization of cell membranes and may eventually end up with lysis. If proteins are affected, these cannot fulfill their enzymatic or structural function.Moreover, oxidative stress is an inducer of inflammatory response. Thus, inflammation in the anterior segment tissues is observed at the early stages of PEX development [13]. The thesis was additionally confirmed by proving elevated serum levels of YKL-40 – a marker of inflammation – in aqueous humor and serum of cataract patients with PEX [14,15]. An exact function of YKL-40

in pathomechanism has not been understood yet, but discovering that would facilitate the preparation of prophylaxis and therapy.

Predisposing factors

Numerous factors may predispose to PEX buildout. Among them genetic factors are crucial. LOXL1 (Lysyl Oxidase-Like 1) polymorphism is significant a risk factor, which has been proven by many authors [16,17,18,19].

This gene encodes an enzyme that is involved in polymerizing tropoelastin monomers into elastin polymers as well as collagen cross-linking. Mainly two altered alleles are responsible for PXF development and those are present in a large proportion of the normal population, in some ethnic groups. Thus, the prevalence ofPEX varies in certain populations [20]. Furthermore, the mutation in FBLN5 gene has recently been identified as a risk factor [21]. Its protein product – fibulin-5 plays a crucial rolein the activation of LOXL1 enzyme. M. Papadopoulou et al. suggest that decreased expression of COX-2 gene may also predispose to PEX development [22]. Although, further research on this subject is required to confirm that hypothesis.

Other non-genetic PEX risk factors include age, female gender, disproportionately high exposure to ultraviolet rays, autoimmune diseases, history of trauma, and viral infections. Interestingly, disproportionately high exposure to ultraviolet rays, e.g. in higher latitudes or specific geographic areas can also accelerate pseudoexfoliative material formation [12,23,24].

Morphology

A variety of terms describing the morphology of pseudoexfoliative material has arisen throughout the years. Authors characterize it as ‘amyloid-like’ or ‘dandruff-like’, greyish matter. Compared to non-PEX patients, those affected by that degenerative disease manifest a reduced corneal cell density as well as decreased corneal sensitivity. There is evidence that decreased corneal sensitivity is caused by an abnormality of subbasal nerve fibers. Furthermore, eyes affected by PXF have a relatively shallow anterior chamber and reduced angle openness during light-induced pupil constriction [25].

Clinical symptoms

Lens

Lens affected by the pseudoexfoliation syndrome (PEX) has three different zones, whichcould be differentiated based on the amount of whitish pseudoexfoliative material (PXM) accumulated on its surface. The most common pattern consists of a central zone, a disk- shaped area, that is usually the size of the pupil, material accumulated is homogenous. The intermediate zone is clear and located between the central and peripheral zones. This zone is clear,with no PXM deposited, as a result of rubbing of the iris over the lens surface. Rubbing is observed during pupillary movement. Peripheral, granular, and the often layered zone is a place of increased accumulation of the pseudoexfoliative material [3,26]. The central zone is variable and might be absent, the intermediate and peripheral zones are always present [3].

Iris

The most common clinical feature regarding the iris is the accumulation of the PXM at the pupillary border. Sphincter atrophy causes the formation of cavities that are resembling moth bites. The loss of the iris pigment, deposition of the PXM by the anterior segment are reflected in the iris sphincter resulting in the transillumination effect [27].

The dispersed pigment is lining itself in the spiral form at the pupillary sphincter and has aless regular pattern at the iris circumference [27].

The vascular abnormalities are also characteristic in PEX. The blood vessels are often narrowed and may become obliterated, their walls can become completely degenerated in the advanced stages of PEX. Small hemorrhages inside of the iris can also be observed as a result of the pharmacological mydriasis [26].

Cornea

On the endothelial surface of the cornea, there could be deposited PXM in the form of flakes. The pigment aggregation on the cornea may result in disseminated and aspecific pigmentationon the central corneal endothelium, infrequently resembling the shape of the Krukenberg's spindle. More often, the pigment deposits itself on the Schwalbe's line as one or many wave- shaped pigmented lines in the outer cornea anterior to the Schwalbe's line [3,27].

The corneal endothelial cells are morphologically changed, their number is reduced, and are prone to decompensation [27]. The central corneal thickness is increased in the eyes affected by the PEX, which might be a sign of early corneal dysfunction [26,28].

Ciliary body and the Zinn nodules

PXM is dispersed and as a result might accumulate on the zonules, weakening them [26]. This weakening causes instability of the whole zonular apparatus alongside the ciliary body andthe lens. This might cause trembling, subluxation, or even lens displacement. It is particularly dangerous during cataract operations, as it might result in the tearing of the ciliary rim withthe vitreous body passage [27].

Systemic disorders accompanying PEX

PEX was primarily identified as a disorder affecting especially the anterior segment of the eyesince first described by Lindeberg [1]. This was believed as the PXM accumulated in the eye can be easily detected - in the patients with the typical PEX. The suspicion that PEX might not only be an ocular phenomenon, was raised when a patient was showing the signs of pigment abnormalities, but without clinical PEX symptoms - these patients are called “PEX suspects” [29]. Research has provided evidence that the PXM might be deposited in the posterior wall of the ciliary artery [30], in the biopsy of skin [31], and various extraocular tissues [32]. These depositions were found in patients affected by PEX, with and without affected eyes. These findings indicated a possibility that PEX might be a systemic disorder [29]. In the study by Ursula M. Schlötzer-Schrehardt et al a case of classic bilateral PEX with a systemic distribution of PXM affecting various organ systems is described. During the autopsy of skin, lungs, heart, kidney, liver, and cerebral meninges, with the use of transmission electron microscopy, typical pseudoexfoliation fibers were identified [33]. The fibers of PXM were mainly found in the connective tissue (CT) components - fibroblasts,collagen, and elastic fibers. This information provides data for the systemic nature of PEX, which involves the CT metabolism throughout the body [29].

Complications - glaucoma with PEX

PXM can be observed mostly at the cornea (Kukenber’s spindle, Schwalbe’s line), pupillary margin, and on the anterior lens surface. Accumulation of the PXM is also present on the zonular apparatus. PEX is known as one of the most common causes of secondary open-angleglaucoma (SOAG), due to the abnormal accumulation of the PXM in the drainage system of the eye [34]. Blockage of the draining system (mainly the trabecular system and Schlemm’s canal) prevents the physiological circulation of the vitreous humor, as a result, causes rapid fluctuations of the intraocular pressure (IOP) [35].

PEX is currently known as the most common cause of open-angle glaucoma (OAG) [26]. Pseudoexfoliation glaucoma (PEG) is characterised by a rapid increase in the IOP and the differences might be enormous. This kind of increase of IOP is particularly dangerous for a patient, as the high-pressure differences are more damaging to the optic nerve disc, rather than increased but stable IOP. IOP in PEG is usually higher than the IOP in the OAG. It also shows high daily fluctuations and a decreased susceptibility to maintenance treatment [35,36]. PEG is now considered to be more dynamic and severe compared to primary OAG (POAG) [26].

High IOP is determined by the blockage of the trabecular meshwork is caused by the pigment pieces produced by the iris during the myiardasis as well as by the PXM. During this accumulation, there are structural changes in the trabecular meshwork and the canal of Schlemm, such as a complete blockage of the canal and a pressure increase in the veins responsible for the aqueous humor drainage [35].

The most common treatment for this kind of glaucoma is a pharmacological lowering of the IOP, when this is not sufficient an operation must be conducted. When the IOP is stabilised, there are still some dysfunctions that might occur like elastotic degeneration of the cribriform plate and the extraocular vessels (for example short posterior ciliary arteries). These dysfunctions increase the sensitivity of the optic nerve for damage and degradation [35,37].

Preoperative diagnostics of PEX-related cataract

Diagnosis of pseudoexfoliation syndrome is primarily based on the examination of the eye with a slit lamp. This study, preceded by a pharmacological extension of the pupil, is a sensitive and specific method to make a diagnosis at an early stage of the development of the disease. The diagnosis is based on the presence of typical gray-white petals on the edge of the pupil and fibrous deposits above the anterior lens bag, located mainly in the area of the pupil hole, often separated from peripheral residues by a clean zone [38]. The peripheral band has a granular structure, a sharply delimited medial border, and numerous radial indentations [27] In case of an advanced cataract, with a dim red glare, the diagnosis of PEX syndrome may be difficult because the grey-white petals do not contrast with the color of the lens affected by the disease [38].

PEX syndrome is a systemic disease of the extracellular matrix so it affects all structures of the anterior segment of the eye, which is associated with a more frequent occurrence of perioperative and postoperative complications. The production and deposition of

pseudoexfoliative material lead to characteristic changes in the corneal endothelium, trabecular meshwork, iris, lens, ciliary body, zonules and the structures of the blood-aqueous barrier [39]. The most important risk factors are zonular instability and poor pupil dilation. These two clinical manifestations of PEX syndrome are believed to be the most important causes of increased risk of lens bag rupture and vitreous loss during cataract surgery [39].

An important step in the preoperative examination of the patient is the assessment of signs of increased zonular weakness. Exfoliation material on the appendages and ligaments of the ciliary body can be detected by high-resolution ultrasound biomicroscopy (UBM). During the examination a thickening of the anterior lens bag and of the fibrous strands of the ciliary zonule as well as exfoliation material on their surface can be observed [40]. This condition can lead to the tremor of the lens, its subluxation or displacement, to the reduction of the depth of the anterior chamber due to the forward displacement of the lens and finally, to the formation of closed- angle glaucoma due to the pupil and ciliary blockade [39]. It may also entail the risk of detachment of the ciliary zonule with the vitreous body loss during cataract surgery [38,40]. The incidence of lens tremor and/or subluxation in the eyes with pseudoexfoliation syndrome ranges from 8. 4% to 10. 6% [39]. The rate of postoperative complications is higher in the eyes with PEX with preoperative and/ or intraoperative signs of zonular weakness undergoing phacoemulsification. It should also be noted that the degree of advancement of changes is primarily correlated with the age of the patient, not necessarily with the amount of pseudoexfoliation material [38].

In the majority of patients with PEX syndrome, poor pupil dilatation can be expected due to infiltration of the iris stroma with the accompanying excessive exfoliation of the extracellular matrix causing mechanical blockage during pupil dilation. The adhesion of the exfoliating material to the pigment epithelium of the iris and the anterior lens bag results in a mechanical restriction of pupil movements [39]. Also the presence of posterior adhesions can cause a reduced response to mydriatics. Before the surgery, it is necessary to assess the degree of maximum pupil dilatation. This makes it possible to take appropriate measures, among which can be distinguished preoperative use of non-steroidal anti-inflammatory drugs, which can help in maintain the maximum extension of pupils during the procedure [38]. It should also benoted that due to sphincter fibrosis, it is recommended to avoid excessive pupil dilation, as it often remains dilated, which predisposes it to pupillary capture [38].

Specular microscopy studies have shown that in patients with PEX, the number of endothelialcells of the cornea is 5-9% lower compared to patients without pseudoexfoliation

syndrome [38,41]. In addition, the morphology of cells also changes. Endotheliopathy in PEX syndrome can result both from the accumulation of exfoliation material between the endothelial cellsand the Descemet membrane, as well as from increased intraocular pressure caused by the blood-aqueous barrier breakdown. Changes in the density and morphology of corneal endothelial cells may be responsible for an increased risk of corneal decompensation after the surgery [38].

Another preoperative problem in pseudoexfoliation syndrome is increased intraocular pressure. PEX is also the most common cause of secondary glaucoma [38]. Patients are more likely to experience an increased intraocular pressure immediately after surgery. For this reason, all viscoelastic material must be carefully removed from the eye during surgery. Patients with extensive visual field loss or severe glaucomatous atrophy of the optic nerve should have tonometry performed 4-6 hours after surgery and sharp increases in intraocular pressure should be treated promptly [39]. In glaucomatous patients, the combined phacoemulsification and trabeculectomy surgery reduces the risk of acute postoperative intraocular pressure increase and has a positive effect on the long-term maintenance of normalIOP [39]. In addition, cataract surgery is likely to protect the eye against the development of glaucoma [38,42].

The table above shows preoperative risk factors, perioperative and postoperative complications associated with PEX syndrome in patients undergoing phacoemulsification procedure [38,39,43].

Preoperative risk factors	Intraoperative complications	Postoperative complications
Narrow pupil, insufficiently responsive to mydriatics	Iris damage	**Implanted lens dislocation**
Weak zonular fibers	Posterior capsule rupture	**Posterior synechiae**
Posterior capsule fragility	Capsular bag dislocation	**Acute intraocular pressure rise**
Pupillary synechiae	Vitreous loss	**Posterior lens capsule opacifiaction**
Vitreous prolapse		**Posterior capsule rupture**
Secondary open angle glaucoma		**Fibrinous uveitis**
Shallow anterior chamber		**Endothelial decompensation**
		Descemet's membrane detachment
		Cystoid macular edema

Cataract phacoemulsification

Phacoemulsification is a method of surgical treatment of the cataract using ultrasound waves. The previously commonly used ECCE method (extracapsular cataract extraction) differs inthe size of the incision and, above all, in the method of removal of the nucleus [44]. In the ECCE method, the opaque nucleus was removed to the outside with a loop and hook orpushed out under pressure on the eyeball [40,44].

In the phacoemulsification method, the opaque nucleus is broken using ultrasounds and then removed with special tools introducedby an incision on the cornea with a width of 2.8-3mm [40,44].

This method was developed in 1967 by Charles David Kelman. At first, this method was associated with a high percentage ofperioperative complications, but with the introduction of improved, modern technologies and tools it became the most commonly performed method of cataract surgery [40].

The procedure begins with an incision of the cornea with a width of 2. 8-3mm. Then a viscoelastic substance is administered into the anterior chamber (to maintain the ventricle and protect the corneal endothelium), a continuous circular capsulorhexis (incision of the anterior lens bag), hydrodissection (that is, separation of the peripheral part of the cortex from the capsule by injection of fluid under it) and hydrodelineation (injection of fluid into the nucleus). Then, with the help of ultrasound, the nucleus of the lens is broken (phacoemulsification), successively followed by irrigation and aspiration of cortical masses, implantation of the lens, careful rinsing of the viscoelastic substance, administration of an antibiotic into the anterior chamber, and finally sealing the corneal incisions (the wound healsitself, does not require the application of stitches) [27,44].

Phacoemulsification tools maintain the balance of fluid flow in the eye during the procedure when ultrasound and vacuum are used. This is extremely important for the safety of surgery due to the small volume of the anterior and posterior chambers of the eye. The inflow and outflow of iris fluid must be controlled to avoid an increase in intraocular pressure. The liquidis removed through the emulsifier tip by a vacuum pump. The head of the device, on the otherhand, provides energy to break down the opaque nucleus. It should be noted that the use of ultrasound has a negative effect on the corneal endothelium and therefore, it is recommended to use the lowest effective amount of energy [40].

This effect can be achieved both by reducing the duration of ultrasound on eye tissues,

and byusing pulsation mode, rather than continuous mode. The technique of the procedure is also important. Currently, two techniques are used – Shepherd's four quadrants technique [40] and chop technique. The technique of 4-quadrants consists of gouging two perpendicular linesinto the shape of a cross, and then breaking the nucleus into four parts [40].

Chop technique is based on dividing nucleus using a special hook (chopper) to fragment it into smaller pieces and remove them using ultrasound.

Cataract phacoemulsification in patients with pseudoexfoliation syndrome - difficulties and technique

Many studies have shown that phacoemulsification in PEX patients is safer than extracapsularcataract extraction and is therefore the technique of choice [39].

Cataract surgery in the presence of pseudoexfoliation syndrome is undoubtedly a special challenge for the operator. The incidence of intraoperative and postoperative complications such as zonular dialysis, rupture of the lens capsule, vitreous loss, and intraocular lens (IOL) decentration is significantly higher in patients with this syndrome. However, the complication rate can be reduced by carefully examining the patient before qualifying for the procedure, using a precise surgical technique with extreme caution and a longer postoperative follow-up period [39,43].

The basic difficulties faced by the surgeon are a narrow pupil, insufficiently responsive to mydriatics, an unstable ligamentous apparatus, and a fragile posterior lens capsule [40]. The frequent occurrence of a dense lens nucleus in PEX patients may also be a problem because this situation will require the use of more ultrasound energy [43].

Narrow pupil, insufficiently responsive to mydriatics

Cataract surgery on the eye with a narrow pupil is demanding for the operator. However, it should be borne in mind that excessive stretching of the pupil may lead to microcracks, increased postoperative inflammation, and even damage to the sphincter muscle, which may result in permanent pupil dilatation. Therefore, such activities should be avoided. In most cases, pupil stretching is not necessary, but if pupil diameter does not exceed 4-4.5mm, it maybe necessary. Mydriasis can be improved by the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the eye drops [38,39]. Then, during the procedure, a mixture of 1% lidocaine

with adrenaline diluted in a ratio of 1/100000 is administered into the anterior chamber. During rupture of the anterior lens capsule (capsulorhexis), the appropriate pupil diameter is obtained by using a highly cohesive viscoelastic substance. The procedure is performed using an ophthalmic viscosurgical device (OVD) or a combination of two such instruments with different rheological properties – dispersive and coherent [38].

First, the dispersion substance is administered first to cover the corneal endothelium, and thencohesive viscoelastic is centrally injected to deepen the anterior chamber, flatten the anterior lens capsule, and achieve adequate pupil dilation to facilitate the anterior lens capsule tearing procedure. The operator should be careful not to over-inflate the anterior chamber and damage the ligamentous apparatus [38]. If posterior synechiae are present, they should be released using capsulorhexis forceps [39] or a blunt spatula [38] before proceeding. Iris retractors can also be used to stretch narrow pupils, but only in situations where they are necessary for a safe procedure [40].

There is also a device such as a pupil dilator ring (for example Malyguin's ring) the advantage of which is that it contributes less to iris injury. It is relatively easy to apply, protects the sphincter muscle from damage, and after its removal, the pupil returns to its normal size [39].

Instability of the ligamentous apparatus

Complications during the procedure of phacoemulsification in patients with PEX syndrome are mainly due to the phenomenon of instability, weakness of the ligament apparatus. The degree of the problem the operator can assess with the start of capsulorhexis. The first sign of reduced tension of the anterior lens capsule is difficulties with its puncture. In case of severe weakening of ligaments, the lens capsule may rupture due to the lack of forces counteracting the pulling of forceps to capsulorhexis leading to too small capsulotomy formation. In such a situation, a technique using a hook can be performed. A hook is placed to catch the already torn anterior lens capsule while continuing capsulorhexis with the forceps. The optimal would be to achieve 5-6 millimeter, continuous, central capsulorhexis [38].

To support the lens capsule during all stages of phacoemulsification, it may be helpful to use acapsular tension ring (CTR). Depending on the weakening of the ciliary zonule or the rupture of the ligament apparatus, the operator may decide to place the ring before or after phacoemulsification of the nucleus and before irrigation-aspiration of the lens cortex [39]. The device allows the lens bag to be evenly stretched and the rupture/stretching areas of the ciliary

zonule elements can be supported by redistributing ligament tension around the capsule. The result is optimal centering of the intraocular lens (IOL). Reports show that the use of the ring during the procedure reduces intraoperative complications in the eyes with PEX syndrome. In cases of milder zonulopathy, the use of CTR may be sufficient to perform manoeuvres safely during the operation and to keep the IOL in the capsule.In more advanced states of weakening of the ligamentous apparatus, the use of CTR alone may not be sufficient to protect the eye against complications such as postoperative lens dislocation. In such situations, the use of lens capsule retractors is recommended when performing hydrodissection and phacoemulsification, followed by implantation and suturing of a modified CTR to ensure the stability of the intraocular lens capsule complex [38,39].

Studies on the safety and efficacy of capsule tension ring implantation in combination with phacoemulsification and intraocular lens implantation in patients with PEX syndrome inpatients who have undergone trabeculectomy surgery have shown that, indeed, correct use of CTR in this situation may have beneficial implications. First of all, decentration of theimplanted intraocular lens is prevented and perioperative complications are reduced [45].

Studies have also shown that implantation of the capsular tension ring in patients with PEX- related cataracts without large zonulysis has no statistically significant effect on the predicted refraction and changes in the depth of the anterior chamber after phacoemulsification. The predicted refractive error has a shift towards hyperopia in both patients with and without the ring implanted [46].

The technique of cataract phacoemulsification in patients with PEX syndrome

The technique of cataract surgery associated with pseudoexfoliation syndrome does not differ significantly from that used routinely in patients without PEX. The stop and chop technique isused because it allows the least possible stress on the ligamentous apparatus, and also limits the surgical maneuvers to the center of the anterior chamber, avoiding the capsule equator andthe pupil [38].

The corneal cut should be slightly larger than during routine surgery as this will facilitate the outflow of the viscoelastic substance and iris fluid from the anterior chamber of the eye, and as a result, will ensure optimal regulation of the pressure exerted on the ligamentous structures and the lens [39].

Capsulorhexis should be performed in such a way that the pressure applied on the anterior capsule is as low as possible. A sharp tool should be used for the initial perforation

because the weakening of the ligamentous apparatus is associated with less stress on the anterior capsule, which makes it difficult to puncture it. If necessary, counterpressure can be exerted with a needle or chopper. Capsulorhexis should be performed within the outer limits of the pseudoexfoliation ring. Its size matters a lot. A diameter that is too small may place additional stress on the ligamentous apparatus [39]. The optimal diameter of capsulorhexis shouldoscillate around 5.5 mm, which means it should be wider than in the eyes without the pseudoexfoliation syndrome [39,40]. As a result, in the future, there will be no shrinking of the capsule. Otherwise, shrinkage forces could lead to it moving into the vitreous chamber [40].

Hydrodissection and hydrodelineation should be carried out carefully so that the pressure exerted on the ligamentous apparatus and the lens is as low as possible. The injection of the irrigation fluid must not be too intense/aggressive as it may aggravate the weakening of the ligaments. Anterior chamber overfilling should also be avoided [39]. The use of a high-density or dispersive viscoelastic substance may result in a capsular block, which may rupture the posterior capsule and displace fragments of it into the vitreous chamber [40]. Lens nucleus phacoemulsification should also be performed with caution. In patients with PEX, the presence of a dense lens nucleus may be problematic, which will require the use of more ultrasound energy [43].

Aspiration of cortical masses is a critical moment in the procedure because the pressure exerted on the zonule of Zinn is the greatest then. The procedure should be performed by tearing off the masses tangentially, avoiding at the same time centripetal movements, which involve putting pressure on the ciliary zonule and the posterior capsule [39]. According to some authors, gentle centripetal flexion may, however, help in the thorough removal of the cortex [38]. In cases where the cortical masses adhere too tightly to the capsule, implantation of an intraocular lens before their aspiration may stabilize the ligamentous apparatus [40]. As mentioned above, implantation of a capsule tension ring (CTR) is a good option. Its presence, however, has a controversial effect on the one hand, facilitating the detachment of the cortex from the capsule, and on the other hand, hindering its aspiration when residual masses are trapped behind the device [38,39]. Abundant and repeated hydration of the cortex can help soften it, enabling effective aspiration [38].

The prolapse of the vitreous body due to a ligamentous defect can occur both before and during surgery. Limited anterior vitrectomy and tamponade using a cohesive ophthalmic viscosurgical device (OVD) can support cataract phacoemulsification and cortical mass aspiration. By filling the anterior chamber with a cohesive viscoelastic substance before

removing the instruments from the eye, it prevents collapsing [38].

Selection of an implanted intraocular lens (IOL)

The choice of an intraocular lens is important for eyes with pseudoexfoliation syndrome andis related to the assessment of the condition and future risk of capsular instability. In the case of a weak ligament apparatus, the surgeon may implant a one-piece or three-piece acrylic lensafter implanting the capsular tension ring. The one-piece IOL requires less surgical manipulation that could damage the capsule or ligaments, so some authors consider it as a product of choice for patients with PEX [38]. According to other authors, implantation of a three-part lens is an equally safe procedure, and at the same time, it may prove to be a better option because the elastic nature of its elements provides tension supporting the maintenance of smaller areas of rupture of the ligamentous apparatus without introducing an additional capsular tension ring [39].

Studies have shown that the use of modified posterior chamber lenses with the heparin-coatedsurface is associated with a lower number of postoperative fibrinoid reactions, a rarer appearance of pigment or cell deposits on the lens, and a lower incidence of posteriorsynechiae compared to other artificial intraocular lenses [39].

Due to the risk of capsular contraction and lens decentration, toric IOLs, as well as multifocal IOLs may contribute to an unsatisfactory early or late postoperative visual assessment [38]. The use of silicone, flexible lenses should also be avoided because they may contribute to the development of capsular contraction syndrome [39]. Disadvantageous effects are also obtainedafter implantation of lenses placed in the sulcus due to the risk of their decentration and posterior dislocation. Angle-supported anterior ventricular lenses shouldn’t be used as well, especially in eyes with glaucoma or corneal endothelial cell abnormalities [38,39].

In case of severe ligament instability and vitreous loss, an alternative option may be to use a sclera or iris-attached lens [39].

Postoperative management

After cataract phacoemulsification, control of intraocular pressure (IOP) is extremely important in patients with PEX. The administration of acetazolamide immediately after surgery and the use of local anti-glaucoma drugs in the postoperative period prevent spikes in intraocular pressure and enable its effective control. In addition, topical application of non- steroidal anti-inflammatory drugs and glucocorticosteroids is important as it prevents

inflammation from developing [38,39]. In the postoperative period, patients should also be monitored for possible complications such as displacement of the intraocular lens, development of glaucoma, or IOL luxation [38].

Postoperative complications

Due to the specificity of their disease and the related perioperative difficulties, patients with PEX syndrome are at risk of more frequent complications after phacoemulsification surgery [38].

The most common postoperative complications include increases in intraocular pressure,displacement of the implanted lens, and anterior chamber inflammation. In addition, long and difficult surgery is often associated with severe uveitis, which can lead to posterior adhesions,capsular contraction, and cystic macular edema [24,38].

Patients with PEX often have a reduced number of endothelial cells which could lead to corneal decompensation. Moreover, cataract surgery in these patients is longer and more complicated, often requiring manipulation on the iris and on the intraocular lens, which also predisposes to the occurrence of this postoperative complication [24,38].

Finally, anterior capsular phimosis and posterior capsular opacification are also significantly more common in eyes with pseudoexfoliation syndrome [24,38].

References

1. Lindberg JG.: Clinical investigations on depigmentation of the pupillary border and translucency of the iris in cases of senile cataract and in normal eyes in elderly persons. Acta ophthalmologica Supplement, 1989, 190, 1–96.
2. Piejko P., Ścisłowicz A., Nowak M., Renke P., Chaniecki P.: Pseudoexfoliation syndrom. Polski Merkuriusz Lekarski, 2018, 268, 164–7.
3. Ariga M., Nivean M., Utkarsha P.: Pseudoexfoliation syndrome. Journal of Current Glaucoma Practice, 2013, 7(3), 118–20.
4. Kalaycı M.: Pseudoexfoliation Syndrome Prevalence in Somali Patients with Senile Cataract. İstanbul Med J, 2020, 21(5), 380–3.
5. Teshome T., Regassa K.: Prevalance of pseudoexfoliation syndrome in Ethiopian patients scheduled for cataract surgery. Acta Ophthalmologica Scandinavica, 2004, 82(3 I), 254–8.
6. Xu Y., Cosmas N., Gartaganis S.: Statistical analysis of pseudoexfoliation syndrome

prevalence, glaucoma and coronary artery disease of the patients with cataract. International Journal of Biomedical Science, 2011, 7(1), 35–43.

7. Aaronson A., Viljanen A., Kanclerz P., Grzybowski A., Tuuminen R.: Cataract complications study: an analysis of adverse effects among 14,520 eyes in relation to surgical experience. Annals of Translational Medicine, 2020, 8(22), 1541–1541.
8. Gunes A., Yasar C., Tok L., Tok O.: Prevalence of Pseudoexfoliation Syndrome in Turkish Patients with Senile Cataract. Seminars in Ophthalmology, 2017, 32(3), 297–301.
9. Dursun F., Vural Ozec A., Aydin H., Topalkara A., Dursun A., Toker M.I., Erdogan H., Arici M.K.: Total oxidative stress, paraoxonase and arylesterase levels at patients with pseudoexfoliation syndrome and pseudoexfoliative glaucoma. International Journal of Ophthalmology, 2015, 8(5), 985–990.
10. Shirakami T., Yamanaka M., Fujihara J., Matsuoka Y., Gohto Y., Obana A., Tanito M.: Advanced glycation end product accumulation in subjects with open-angle glaucoma with and without exfoliation. Antioxidants, 2020, 9(8), 1–11.
11. Schlötzer-Schrehardt U.: Oxidativer stress beim pseudoexfoliationsglaukom. Klinische Monatsblatter fur Augenheilkunde, 2010, 227(2), 108–13.
12. Ferreira SM., Lerner SF., Brunzini R., Evelson PA., Llesuy SF.: Antioxidant status in the aqueous humour of patients with glaucoma associated with exfoliation syndrome. Eye, 2009, 23(8), 1691–1697.
13. Zenkel M., Lewczuk P., Jünemann A., Kruse FE., Naumann GOH., Schlötzer-Schrehardt U.: Proinflammatory cytokines are involved in the initiation of the abnormal matrix process in pseudoexfoliation syndrome/glaucoma. American Journal of Pathology, 2010, 176(6), 2868–2879.
14. Türkyilmaz K., Öner V., Kirbas A., Sevim MS., Sekeryapan B., Özgür G., Durmus M.: Serum YKL-40 levels as a novel marker of inflammation and endothelial dysfunction in patients with pseudoexfoliation syndrome. Eye (Basingstoke), 2013, 27(7), 854–859.
15. Gonen T., Guzel S., Keskinbora K.H.: YKL-40 is a local marker for inflammation in patients with pseudoexfoliation syndrome. Eye (Basingstoke), 2019, 33(5), 772–776.
16. Pasutto F., Krumbiegel M., Mardin C.Y., Paoli D., Lämmer R., Weber B.H.F., Kruse F.E., Schlötzer-Schrehardt U., Reis A.: Association of LOXL1 common sequence variants in german and italian patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Investigative Ophthalmology and Visual Science, 2008, 49(4), 1459–1463.

17. Schlötzer-Schrehardt U., Pasutto F., Sommer P., Hornstra I., Kruse F.E., Naumann G.O.H., Reis A., Zenkel M.: Genotype-correlated expression of lysyl oxidase-like 1 in ocular tissues of patients with pseudoexfoliation syndrome/glaucoma and normal patients. American Journal of Pathology, 2008, 173(6), 1724–1735.
18. Schlötzer-Schrehardt U.: Molecular pathology of pseudoexfoliation syndrome/ glaucoma - New insights from LOXL1 gene associations. Experimental Eye Research, 2009, 88(4), 776–785.
19. Sharma S., Chataway T., Burdon K.P., Jonavicius L., Klebe S., Hewitt A.W., Mills R.A.,Craig J.E.: Identification of LOXL1 protein and Apolipoprotein E as components of surgically isolated pseudoexfoliation material by direct mass spectrometry. Experimental Eye Research, 2009, 89(4), 479–485.
20. Greene A.G., Eivers S.B., Dervan E.W.J., O'Brien C.J., Wallace D.M.: Lysyl Oxidase Like1: Biological roles and regulation. Experimental Eye Research, 2020, 193.
21. Padhy B., Kapuganti R.S., Hayat B., Mohanty P.P., Alone D.P.: De novo variants in an extracellular matrix protein coding gene, fibulin-5 (FBLN5) are associated with pseudoexfoliation. European Journal of Human Genetics, 2019, 27(12), 1858–1866.
22. Papadopoulou M., Papadaki H., Zolota V., Gartaganis S.P.: Immunohistochemical Profiles of LOXL-1, FBN1, TGF-β1, and COX-2 in Pseudoexfoliation Syndrome Current Eye Research, 2017, 42(6), 880–889.
23. Kurtul B.E., Kurtul A., Altiaylik Ozer P., Kabatas E.U., Ertugrul G.T.: Serum Lipid Levels in Pseudoexfoliation Syndrome. Seminars in Ophthalmology, 2017, 32(3), 281–284.
24. Sangal N., Chen .TC.: Cataract surgery in pseudoexfoliation syndrome. Seminars in Ophthalmology, 2014, 29(5–6), 403–408.
25. Zheng X.: New findings for an old disease: Morphological studies on pseudoexfoliation syndrome-related keratopathy and binocular asymmetry. Cornea, 2013, 32 Suppl 1, S84-890.
26. Tekin K., Inanc M., Elgin U.: Monitoring and management of the patient with pseudoexfoliation syndrome: Current perspectives. Clinical Ophthalmology, 2019, 13, 453–464.
27. Kański J.: Okulistyka Kliniczna. [w:] Okulistyka Kliniczna. Górnicki Wydawnictwo Medyczne, Wrocław, 2005, 229–231.
28. Puska P., Vasara K., Harju M., Setala K.: Corneal thickness and corneal endothelium in

29. normotensive subjects with unilateral exfoliation syndrome. Graefe's Archive for Clinical and Experimental Ophthalmology, 2000, 238(8), 659–663.
30. Prince A.M., Streeten B.W., Ritch R., Dark A.J., Sperling M.: Preclinical diagnosis of pseudoexfoliation syndrome. Archives of Ophthalmology, 1987, 105(8), 1076–1082.
31. Aasved H., Seland J.H., Slagsvold J.E.: Timolol maleate in treatment of open angle glaucoma. Acta Ophthalmologica, 1979, 57(4), 700–708.
32. Airaksinen PJ.: The long-term hypotensive effect of timolol meleate compared with the effect of pilocarpine in simple and capsular glaucoma. Acta Ophthalmologica, 1979, 57(3), 425–434.
33. Ritch R., Podos S.: Laser trabeculoplasty in the exfoliation syndrome. Bulletin of the New York Academy of Medicine: Journal of Urban Health, 1983, 59(4), 339–344.
34. Schlötzer Schrehardt U.M., Koca M.R., Naumann G.O.H., Volkholz H.: Pseudoexfoliation Syndrome Ocular Manifestation of a Systemic Disorder? Archives of Ophthalmology, 1992, 110(12), 1752–1756.
35. Samples JR., Konstas T.: Exfoliative Glaucoma. https://www.glaucoma.org/glaucoma/exfoliative-glaucoma.php (cited: 20.04.2021).
36. Zieliński M., Turno-Kręcicka A.: Jaskra w zespole pseudoeksfoliacji. Przegląd Okulistyczny, 2008, 6(26), 1–2.
37. Jeng S.M., Karger R.A., Hodge D.O., Burke J.P., Johnson D.H., Good M.S.: The risk of glaucoma in pseudoexfoliation syndrome. Journal of Glaucoma, 2007, 16(1), 117–21.
38. Mitchell P., Wang J.J., Hourihan F.: The relationship between glaucoma and pseudoexfoliation: The blue mountains eye study. Archives of Ophthalmology, 1999, 117(10), 1319–1324.
39. Fontana L., Coassin M., Iovieno A., Moramarco A., Cimino L.: Cataract surgery in patients with pseudoexfoliation syndrome: Current updates. Clinical Ophthalmology, 2017, 11, 1377–1383.
40. Kaštelan S., Tomić M., Kordić R., Kalauz M., Salopek-Rabatić J.: Cataract Surgery in Eyes with Pseudoexfoliation (PEX) Syndrome. Journal of Clinical & Experimental Ophthalmology, 2013, S1.
41. Zalewski D.: Ocena ryzyka operacyjnego leczenia zaćmy metodą fakoemulsyfikacji u pacjentów z zespołem rzekomego złuszczania. Gdański Uniwersystet Medyczny, Gdańsk, 2015.

42. Hasegawa Y., Mori Y., Sakisaka T., Minami K., Miyata K., Oshika T.: Risk factors for corneal endothelial cell loss by cataract surgery in eyes with pseudoexfoliation syndrome. Clinical Ophthalmology, 2016, 10, 1685–1689.
43. Kristianslund O., Østern A.E., Räen M., Sandvik G.F., Drolsum L.: Does cataract surgery reduce the long-term risk of glaucoma in eyes with pseudoexfoliation syndrome? Acta Ophthalmologica, 2016, 94(3), 261–265.
44. Potyomkin V., Potyomkin V.V., Goltsman E.V.: Cataract surgery in pseudoexfoliation syndrome. Ophthalmology Journal, 2020, 13(1), 37–42.
45. Grzybowski A.: Okulistyka. Edra Urban&Partner, Wrocław, 2018, 153–154.
46. Zhang Y., Zhang F., Maimaiti T., Kasimu D., Jiang Y.X.: Clinical application of capsular tension ring on cataract surgery in patients with pseudoexfoliation syndrome after trabeculectomy. International Eye Science, 2014, 14(9), 1627–1629.
47. Mohammad M., Sadegh K., Farideh S., Farshad O., Rad A.M., Mirdehghan M.S.: Effect of capsular tension ring implantation on predicted refractive error after cataract surgery in patients with pseudoexfoliation syndrome. International Journal of Ophthalmology, 2020, 13(4), 587–590.

Mohs Micrographic Surgery as a way to a good quality of life for nowadays ophthalmicpatients

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Abbreviation list

- AUC- Mohs Appropriate Use Criteria
- BCC- basal cell carcinoma
- CNS- Central Nervous System
- MMS- Mohs micrographic surgery
- SCC- squamous cell carcinoma
- SGC- sebaceous gland carcinoma
- UV- ultraviolet
- WLE- wide local excision

Introduction

The eyelids are one of the essential accessory organs of the eye. They are responsible for the protection of the anterior eyeball surface from harmful factors [1].

The covering skin is considered to be the thinnest and most sensitive skin on the whole body [2].

Skin malignancies are a significant challenge for contemporary dermatologists, surgeons, oncologists, pathomorphologists, and ophthalmologists.

The eyelid is a controversial location because of its proximity to a vital sensory organ- the eye, as well as the central nervous system (CNS). Therefore, the treatment of the mentioned malignant tumors in the first place mainly involves surgical treatment. The main goal considered by specialists is to preserve the tumor-affected eyelid's functionality and aesthetics [3].

One of the innovative surgical methods is MOHS surgery, which was introduced already in the 1930s [3]. Its innovator was surgeon Dr. Frederic E. Mohs [4]. This method wasbased on the excision of the skin parts occupied by the neoplastic process, fixation with zinc chloride paste (now frozen) *in situ*, and then excision of subsequent stages of the examined surgical margins until complete removal of the tumor. The results of this novel technique wereencouraging, as according to Dr. Mohs' study, 93% of nonmelanoma skin cancers, including many advanced ones, were successfully cured [5]. The procedure brought many benefits ranging from sparing nonmelanoma tissues nearby, ensuring the functionality and aesthetics of a given organ to the potential possibility of curing previously untreatable cancers.

Epidemiology

It is estimated that 5-10 % of all malignant skin cancers and 15 % of facial cancers are localized in the periocular [6].

Basal cell carcinoma (BCC) is the most common,while squamous cell carcinoma (SCC), sebaceous gland carcinoma (SGC), malignant melanoma are less prevalent [7].

The prevalence varies by geographic region. For example, in the United States in 2017, the rate was about 16 cases per 100,000 inhabitants per year, while in Singapore, it was about three times less- 5.1 per 100,000 per year. BBC accrues the largest percentage of all malignancies localized on the eyelids: 85-95%, followed by SCC: 3.4-12.6%, SGC: 0.6-10.2%. The smallest percentage is malignant melanoma and Merkel cell carcinoma accounting for less than 1%. A higher incidence of SCC by more than 3.5 times was observedin men (2.4 per 100,000 inhabitants per year) [8].

Clinical aspect of eyelid malignancies

Both the patient and the specialist may be worried by a change in the shape of the eyelid margin. The appearance of ulceration, induration, new color, or loss of tenderness/sensitivity of

the tissue suggests beginning the diagnosis [1,7]. In many cases, loss of eyelashes, flesh-colored or pink pearly papules, the presence of dilated small blood vessels,scar formation, non-healing pustules, secondary ectropion as well as eyelid retraction are noted [7,9].

In most cases of eyelid malignancies, exposure to ultraviolet radiation (UV) is a significant risk factor [8]. Other predisposing factors for malignant lesions include vitiligo, chronic skin lesions, and genetic skin disorders such as xeroderma pigmentosum and epidermodysplasia verruciformis [9]. The reported malignant eyelid lesions have a high risk of recurrence and metastasis. The medial canthus of the eye is a particularly susceptible site for deep neoplastic growth, which can be explained by the embryologic cleavage plane occurring there, which is more easily penetrated by the cells [10]. Tumor invasion in the ocular region is usually silent, which hinders rapid diagnostics. Furthermore, it exacerbates prognosis because the area of tumor spread may also involve the intracranial region [7].

Diagnosis

Assessment of the nature of malignancy and the depth of neoplasm growth significantly impacts the type of treatment and prognosis. The diagnosis of malignant eyelid lesions itself does not pose significant problems nowadays. However, their further qualification as malignancy is already a major challenge requiring the experience of a specialist as well as the ability to perform accurate examinations. Malignant lesions may mimic benign ones and vice versa; this is the case of, e.g., SGC resembling chalazion or cystic basal cell carcinoma (BCC) often mistaken for hidrocystoma. A pigmented hidrocystoma may erroneously be considered a malignant melanoma [7].

The standard classification of tumor staging is TNM (tumor, nodus, metastases). In the case of tumors localized on the eyelids, the malignancy is determined based on anatomical features of the ocular region. In melanomas, their origin and extent are determined and the TNM scale for melanomas of the skin or conjunctiva is also used [3].

In most cases, an incisional biopsy is used at the outset to identify the type of eyelid malignancy.

At this stage, it is very important for the specialist to properly collaborate withthe pathologist and provide crucial information regarding the observed lesion and the patient's history. A diagnostic exception is the management of a suspicious SGC. In this case, a biopsy covering the entire thickness of the eyelid is recommended. These biopsy specimens should be

immersed in a saline solution that allows Oil Red O and Sudan Black staining for lipids. In addition, map biopsies are used in cases of doubtful intraepithelial spread of SGC [8].

Surgical treatment

The most popular treatment options for eyelid cancer include wide local excision (WLE) and Mohs Micrographic Surgery (MMS). The choice of treatment technique depends on the patient's age, tumor stage, location, size, presence of metastases, and patient history, among other factors. For WLE, the margin is several mm depending on the type of cancer. Most specialists specify 3-4 mm as the margin for BCC, 4-6 mm for SCC and SGC, lentigo maligna and melanoma *in situ* 5-6 mm. For thin melanomas, this can be as much as 10 mmfor tumors with a Breslow thickness of 2 mm or more [7]. When we are concerned with maximal protection of healthy tissues in the neighborhood of tumor-lesioned cells, the possibility of subsequent eyelid reconstruction, and minimizing the likelihood of recurrence, treatment using the MMS technique is recommended. It is primarily recommended in cases ofperiocular nonmelanoma skin cancer [11,12]. Any mistake made in the management can havevery adverse effects on the patient's health and life. Therefore, the MMS technique is most commonly used to treat eyelid tumors. Treatment with this technique belongs to one-day surgery without the need for general anesthesia. The Mohs Appropriate Use Criteria (AUC) scale is used to determine the usefulness of this technique based on location, characteristics ofthe tumor-affected tissue, and the patient himself.

Locations where MMS is used, include the face, eyelids, eyebrows, nose, lips, chin, ear, genitals, hands, feet, ankles, fingernails and nipples. It is also recommended for immunologically deficient patients with genetic syndromes such as xeroderma pigmentosum, who have had previous skin irradiation, have been diagnosed with high-risk cancers, and have positive margins at the last excision. Aggressive histologic subtypes along with features such as poorly differentiated cells or undifferentiated cells, in perivascular locations, with spindle cells present, involving a Breslow depth of 2 mm or greater, Clark level IV or higher are particular indications for this type of therapy [12].

Table 1 presents the Clark and Breslow classification and risk for metastasis [13,14, 15].

Depending on the diagnosis, treatment options such as cryotherapy, photodynamic therapy, electrical resection, radiation therapy, local or systemic chemotherapy and immuno-

therapy are also used for therapeutic purposes [3].

Table 1. Clark and Breslow staging and risk

Clark scale (level of invasion)		**Breslow scale (vertical thickness)**	**Risk for metastasis**
I	Epidermis (*in situ*)	***In situ***	**None**
II	Invasion of the papillary dermis	< 0,75 mm	Minimal
III	Filling of the papillary dermis but not extending to the reticular dermis	0,75- 1,5 mm	Significant/ medium
IV	Invasion reticular dermis	1,51- 4,0 mm	High
V	Invasion subcutaneous fat/ tissue	> 4,0 mm	Extremely high

Necessary surgical equipment in the MMS technique includes a scalpel, fine forceps, scissors, gauze, and an electrosurgical device for coagulation. We additionally use needle holders, scissors, fine forceps, skin hooks, and a scalpel to reconstruct the area. Some laboratories also have special staining machines and equipment for immunohistochemical staining [5].

The core team of MMS specialists includes a surgeon with an assistant and a histotechnician [5]. In addition, the significant experience of the laboratory technician prevents numerous mistakes [16].

At the beginning of the operation, the doctor marks the extent of the area to be excised and then anesthetizes the area and removes it with a blade or scalpel. The removed tissues should be carefully marked in relation to these orientations; for this purpose, hematoxylin and eosin (H&E) and, less commonly, toluidine blue is used. In the next step, the specialist cuts at an angle of 45 degrees thin margins - peripherally and in-depth [5].

They are successively cut into smaller parts and color-marked to determine the orientation andflattened so that all layers are at the same level [5]. The tissues prepared in this way arefrozen, cut, and prepared horizontally, which facilitates the observation of all cells under the microscope [5,7].

When a neoplastic fragment is found in the observed margins, a fragment corresponding to the patient's neighboring tissues is marked and removed. Thewhole operation is repeated until the margin contains only healthy cells [5].

To proceed with eyelid reconstruction, it is necessary to ensure that there are no neoplastic cells in the tissue after tumor removal. The method's effectiveness depends on the continuity of

growth and integrity of the tumor in question. For minor defects under 25%, closure with sutures or directly leaving the area to heal is usually sufficient [7, 10].

Reconstruction of more extensive wounds often requires restoration of the original tissue formwith a skin flap or skin graft. Skin flaps are more popular because they are better vascularized, shrink more minor, and show high similarity in structure and color. By their utility, we spare other tissue areas that are the donor area for skin grafting [7].

Complications associated with MMS include bleeding, pain, or tenderness of the surgical site and infection. Rarely, numbness of the operated tissues due to cutting smallnerve endings, itching, or keloid - enlarged scar - may also occur. However, these are no different from complications with any other surgical intervention [17].

Conclusions

Our review article aims to show how important it is to introduce new treatment methods to the medical world—referring to the past when a patient diagnosed with progressive cancer died without the possibility of rescue. Nowadays, the progress of medicine gives a very high guarantee for the possibility of returning to thefullness of life and enjoying it for many years to come.

The best treatment for most eyelid tumors is surgical resection with clean margins, which is MMS [8]. Although this technique is time-consuming, expensive, andrequires the involvement of two specialists, it shows higher efficiency. In addition, it provides a better prognosis for the patient, protecting against loss of vision or even life. Unfortunately, currently, MMS is not widely available, which hinders rapid access to a specialist and treatment [7].

One of the most significant advantages is that it belongs to one-day surgery, and the patient is not affected by the side effects of general anesthesia.

Mohs surgery provides a high cure rate for eyelid tumors with maximum sparing of healthy tissue [17].

It is characterized by the lowest recurrence rates in skin cancer treatment- for primary basal cell carcinoma (BCC), it is up to 99% for a 5-year cure rate, and in recurrent BCC up to 94%. This repeatedly ensures the proper functioning of the eyelid, protects the organ of vision, allows the potential preservation of essential structures such as the lacrimal apparatus, and prolongs the patient's life. It proves that MMS should bea gold standard for treating skin cancers, especially those located in the ocular region.

References

1. Machalińska A., Zakrzewska A.: Anatomia oka i układu wzrokowego [in:] Okulistyka. Grzybowski, A. (red.). Wyd. Edra Urban & Partner, Wrocław, 2018, 13-21.
2. https://www.columbiaeye.org/eye-library/eyelid-cancer, Eyelid Cancer, (cited: 15.05.2021).
3. Varde M., A., Murali Krishnan V., Wiechens, B.: Operative Therapie von Lidtumoren, 21 August 2018, History of Mohs Surgery, https://www.mohscollege. org/about/about-mohs-surgery/history-of-mohs-surger (cited: 15.05.2021).
4. Christensen S.R., Leffell D.J.: Chapter 204: Mohs Micrographic Surgery [in:] Fitzpatrick's Dermatology, 9e. Kang, S., Amagai, M., Bruckner, A., L., Enk, A., H., Margolis,D., J., McMichael, A., J., Orringer, J., S. (ed.). McGraw Hill Education, 2019.
5. Yu S., Zhao Y., Zhao H., Lin J., Tang X.: A retrospective study of 2228 cases with eyelid tumors. Internal Journal of Ophthalmology, 2018, 18, 11(11), 1835-1841.
6. Rene C.: Oculoplastic aspects of ocular oncology. Published online 2012, 27(2), 199-207.
7. Silverman N., Shinder R.: What's New in Eyelid Tumors? Asia-Pacific Journal of Ophthalmology (Phila), 2017, 6(2), 143-152.
8. Burgic M., Iljazovic E., Nadarevic Vodencarevic A., Burgic M., Rifatbegovic A., Mujkanovic A., Halilbasic M., Sinanovic M.: Clinical Characteristics and Outcome of Malignant Eyelid Tumors: A Five-Year Retrospective Study. Medical Archives, 2019, 73(3), 209–212.
9. Mori W., Demer A., Mattox A., Maher I.: Mohs Micrographic Surgery at Challenging Anatomical Sites. Dermatolologic Surgery, 2019, 45 Suppl 2, S142-S154.
10. Zhou C., Wu F., Chai P., Shi Y., Ye J., Shi X., Tan J., Ding Y., Luo Y., Esmaeli, B., Jia R., Fan X.: Mohs micrographic surgery for eyelid sebaceous carcinoma: A multicenter cohort of 360 patients. Journal of American Academy of Dermatology, 2019, 80(6), 1608-1617.e1.
11. Prickett, K., Ramsey, M.: Mohs Micrographic Surgery, February 2021, Bookshelf ID: NBK441833.
12. Ajay A., Dr. Nandhini, Ahmed, S.: Oral malignant Melanoma - a brief review. International Journal of Scientific Research, 2019, 8(6), 2277 – 8179.
13. Breslow's Depth of Invasion (Thickness), https://training.seer.cancer.gov/melanoma/abstract-code-stage/staging.html, (cited: 15.05.2021).

14. Clark and Breslow staging, https://www.cancerresearchuk.org/about-cancer/melanoma/stages-types/clark-breslow-staging , (cited: 15.05.2021)
15. Kozioł, M., Bieniek, A.: The specificity of histological techniques of frozen sections in Mohs Micrographic Surgery. Forum Dermatologicum, 2015, 1(1), 6-11
16. https://www.mayoclinic.org/tests-procedures/mohs-surgery/about/pac-20385222, Mohs surgery, (cited: 15.05.2021).
17. O'Halloran L., Smith H., Vinciullo C.: Periocular Mohs micrographic surgery inWestern Australia 2009-2012: A single centre retrospective review and proposal for practice benchmarks, The Australasian Journal of Dermatology, 2017, 58(2), 106-110.

Medical and non-medical aspects of primary immunodeficiencies

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Introduction

Primary immunodeficiencies also called inborn errors of immunity (IEI), represent a group that mostly consists of about 400 genetic diseases [1]. They are associated with congenital abnormalities in the functioning of the immune system [2]. As a result of these conditions, there is an increased susceptibility to infectious diseases and autoimmune diseases, inflammation, allergies, and neoplasm [3,4].

Primary immunodeficiencies are classified in the most recent report published by the International Union of Immunological Societies (IUIS) in 10 groups:

1. immunodeficiencies that affect cell and humoral immunities
2. immunodeficiencies combined with associated characteristics of immunodeficiencies combines with associated characteristics or syndromes
3. predominantly antibody deficiencies
4. immune dysregulation disease
5. quantitative or functional phagocyte defects
6. innate immunity defects
7. autoinflammatory disease
8. complement system deficiencies
9. bone marrow failure or insufficiency
10. IEI phenocopies [5].

Epidemiology

Primary immunodeficiencies are rare or even super rare diseases that affect approximately 1 in 10 000 children. It is estimated that ca. 6 million patients worldwide suffer from this

condition, but they are rough estimates because this number contains both diagnosed and undiagnosed cases [6].

According to recent research, over 70 - 80% of patients remain undiagnosed, and that's why the actual prevalence remains unclear. There are two age groups when PID is usually diagnosed: when the patient is between 5-19-year-old which is the case in 38% of patients, and surprisingly when the patient is over 40, that gives 22% [7].

PID cases are reported in the registry of the European Society For Immunodeficiencies (ESID). For the Polish population, the prevalence rate is 1,44/100 000 inhabitants [6].

In Poland, there are over 4000 new cases of PID diagnosed yearly, but with the number of cases that remain undiagnosed, that number most likely reaches 20 000 patients total. Statistically, more men (57%) than women (43%) suffer from PID [7].

The most common PID is Selective IgA deficiency which provides diagnostic problems because patients produce other types of immunoglobulin; that's why they are still susceptible to infections, but they appear clinically as mild gastrointestinal infections or appear generally healthy [8].

Genetic Predisposition & Family history

PIDs are a heterogeneous group of diseases in the predominant part caused by monogenic mutation, which leads to the situation when an encoded protein loses its expression, loses its function, or gains a new function [3]. Even within one condition, there are different, overlapping pathomechanisms, and it happens that even for clinically diagnosed conditions, the genetic defect remains unknown [9].

PIDs are caused by inherited genetic defects, or a multifactorial happened. Additionally, communities with a practice of consanguinity have a high rate of PIDs. Family history is positive in roughly 66% of all patients [10]. There are over 430 inborn errors of immunity that result in clinical symptoms [1]. In ten warning signs of PIDs, family history is one of the components. Later studies found that family history is a strong identifier and leads to quick diagnosis and allows to start treatment and prevent serious complications [11].

Diagnosis of primary immunodeficiency

Immunodeficiency should be suspected in the case of patients with severe, unusual,

recurring infections. The kind of test is chosen based on most presumably diagnosis, which depends on symptoms and frequency of particular immunodeficiency [12]. Basic diagnostic procedures consist of complete blood counts, serologic tests of immunoglobulin levels, vaccine titers, and complement levels [13]. They allow evaluation numbers and functioning of elements of the immune system [14].

In addition, there are tests to detect HIV, even though this virus causes secondary immunodeficiency. Negative results of these tests are an indication for wide diagnostics towards immunodeficiency. Results of these tests are pointers for further research, but sometimes they can give answers about the type of immunodeficiency without other examinations. In case of correct results of tests accompanying unclear symptoms and suspicions of immunodeficiency, consultation of immunologists should be recommended. In some types of immunodeficiency (for example, specific antibody deficiency, complement deficiency, chronic granulomatous disease), more specific examinations are necessary [12].

In prime immunodeficiency, we can use flow cytometric-based assays, which enables rating:

- immune cell function (e.g., neutrophil oxidative burst, NK cytotoxicity),
- intracellular cytokine production (e.g., TH17 production),
- cellular signaling pathways (e.g., phosphor-STAT analysis),
- protein expression (e.g., BTK, Foxp3).

Also, genetic testing is gaining importance in the diagnosis of primary immunodeficiency because of the fact that recently more and more primary immunodeficiencies are being defined [13].

During diagnostic procedures also target microbiological tests should be included with taking into consideration possible unreliable negative results of serological tests for viruses and bacteria in case of antibody deficiency. Also, interferon-γ release assays can be false negative in immunosuppressed patients [12].

Quality of life

Knowledge of primary immunodeficiencies is not sufficiently widespread. Even some doctors do not know much about them. It leads to the situation when patients must wait a long time for a referral to an immunological clinic and also for the diagnosis [15].

A recent analysis of the cohort, which concerned 2212 patients with CVID, showed that respectively each year of delay in diagnosis leads to an increased of about 1.7 % risk of death. A similar situation was with each year of increased age at diagnosis - here is a 4.5 % increase in risk [16].

In the case of children, it is connected with absenteeism from school, isolation from peers and hence with the weakening of social ties, and with learning backlogs. After several long hospitals stays over the course of a year, they also have higher rates of depressive and anxiety symptoms. Additionally, it happens that parents quit their job to look after their children, which means that the family loses one of the sources of income. In the case of adults, it is associated with absence from work, reduced salary, and contacts with co-workers, as well as a sense of exclusion. Many of them feel anxious when they leave the house because they may develop an infection the next day. Moreover, patients often think that they suffer from serious, deadly diseases, which affect their psyche even more [15].

It also may be difficult to tell relatives or partners about the disease. People with primary immunodeficiency should assure their partners that there is no connection between their condition and HIV infection and that the disease is not infectious [14].

Another problem is the application of a strict hygiene regime - especially hand washing, oral hygiene, and proper treatment of wounds and scratches. It is also important to remember safe sex requirements, which can help you avoid sexually transmitted infections [14].

Patients also should not smoke because it reduces the risk of infection and lung disease [14].

They also should have a nutritious and balanced diet, the right amount of sleep, and undertake physical activities appropriate to the patient's condition in order to strengthen immunity [14].

Patients with PID are allowed to travel, but they must take certain precautions. Before departure, they should consult an immunologist, among other things, about preventive vaccinations [14].

Doctors should inform them that they can not use live attenuated bacterial vaccines, for example, against yellow fever [14].

They also should have all the necessary medicines with them if they are not available in the country visited - here helpful will be a written certificate issued by an immunologist, directed to the border and medical services of countries [14].

Complications

The problem is underestimated, and the patient takes a lot of inadequately prescribed medications, especially antibiotics, which are associated with their various side effects [15]. Replacement therapy with immunoglobulins causes few side effects, including dizziness and allergy symptoms. Complications are usually short-lived and inedible, but long intravenous administration of immunoglobulins can cause local damage to the veins over time [14].

Due to frequent respiratory tract infections - pulmonary fibrosis, vascular and granulomatous changes may occur. In some cases, primary immunodeficiency can lead to death due to permanent post-inflammatory changes [16-19].

PID can also result in cancer - which affects not only the lungs but also the stomach, breasts, bladder, and cervix.

In addition, autoimmune diseases may develop. It most often affects [14]:

- the joints (pain, inflammation, rash),
- intestines (inflammatory disease),
- red blood cells (hemolytic anemia).

Patients suffering from ataxia-telangiectasia syndrome experience many symptoms related to disorders of the central nervous system - such as problems with eyesight, speaking, swallowing, and balance [20].

Complications connected with BCG vaccine

Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated bacterial vaccine obtained from Mycobacterium bovis [21].

The vaccine protected against meningitis and disseminated TB in children but does not prevent primary infection and reactivation of latent pulmonary infection, which is the main source of spreading infections among people [22]. Presently, the only available vaccine is the one protecting against TB complications. BCG vaccination is recommended by the World Health Organization (WHO) for infants in countries with a high incidence of tuberculosis and in other countries in cases of high risk of tuberculosis. Despite positive effects, adverse events may occur [21]. Various complications depend on BCG strain type, physical-chemical property, bacillary load, administration method, and the host's immune characteristics may occur [23].

One of the risk factors, in this case, is underlying primary immunodeficiency [21]. The danger in case of this vaccination is caused by using live bacteria in vaccination and very early age of the patient, which does not allow to observe symptoms of immunodeficiency. The incidence of complications connected with BCG vaccination in the general population has been estimated at around 1 in 2500 vaccines for localized complications (BCGitis) and 1 in 100,000 for disseminated BCG disease (BCGosis), but patients with Primary Immunodeficiencies (PID) are exposed to developing severe morbidities and mortality [24,25].

Indications of WHO are to give one dose of vaccine to all healthy newborn just after birth. Lack of symptoms in severe combined immunodeficiency causes that infants with this condition are vulnerable to complications after vaccination. The risk of adverse experiences can be reduced by early diagnosis of primary immunodeficiency owing to the newborn screening programs for primary immunodeficiency diseases. Unfortunately, these programs are not commonly available, so protection of newborns from sequelae is achieved by deferring vaccination until excluding the possibility of primary immunodeficiency diseases. This can delay vaccination for 2–6 months after delivery but is advantageous in the protection of BCG complications [24].

How to improve the recognizability

At various conferences, immunologists ask especially family doctors who are first with patients to be vigilant [15]. Attention should be paid to the following warning signs of primary immunodeficiency in children:

1. Four or more new ear infections within one year.
2. Two or more serious sinus infections within one year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within one year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in the mouth or fungal infection of the skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections, including septicemia.
10. A family history of primary immunodeficiency [26].

During the interview, attention should be paid to:

1. Information on preventive vaccinations.
2. Low birth weight, body length (Nijmegen syndrome, growth disturbance).
3. Prolonged fall off of the umbilical cord stump (LAD syndrome).
4. Previous infection.
5. Recurrent, chronic diarrhea (SCID).
6. Tendency to petechiae and ecchymoses (Wiscott-Aldrich syndrome).
7. Heart defect, electrolyte disturbances, seizures (DiGeorg's syndrome).
8. Neurological disorders of the type of ataxia (Ataxia-Telangiectasia syndrome).
9. Microcephaly (Nijmegen syndrome).
10. "Cafe-au-lait" skin spots (AT, Nijmegen syndrome).
11. Skin and organ abscesses (CGD).
12. Severe dermatitis in an infant (Omenn's syndrome).
13. Dermatitis and abscesses (Job's syndrome).
14. Family history: severe infections in relatives, early deaths due to infections, confirmed immunodeficiency in siblings.

During the physical examination should be taken into account:

1. General appearance: impression of a chronically ill child (SCID).
2. Low body weight (Nijmegen syndrome).
3. Short stature (Nijmegen syndrome).
4. Incorrect body proportions (short limb dwarfism with immunodeficiency, hypoplasia of cartilage and hair).
5. Partial eye and cutaneous albinism and mental retardation (Chediak-Higashi syndrome).
6. Facial dysmorphism: wide set eyes, low set ears, underdevelopment of the mandible - (DiGeorge syndrome).
7. Examination of the skin:
   -blotchy rashes, petechiae (Wiscott-Aldrich syndrome),
   -Abscesses (CGD),
   -Chronic eczema (Job's syndrome, Omenn's syndrome).
8. Assessment of lymphatic organs:
   -no tonsils or cervical lymph nodes (Bruton-type agammaglobulinemia),
   -enlarged (CVID).

9. Eye examination - conjunctivitis, telangiectasia (AT).
10. Eardrums: scars and perforations (CGD, subclass deficiency - IgG).
11. Oral cavity: candidiasis, periodontitis (SCID, CGD).
12. Chronic persistent rales (CVID).
13. Palpation of the liver and spleen: (CVID, SCID, hyper IgM).
14. Symptoms of arthritis, restricted mobility (CVID).
15. Movement incoherence, intentional tremors, masked face (AT) [20].

Course of Covid 19 in people with primary immunodeficiency

Most patients with PID have the same COVID-19 symptoms as people without immunodeficiency. Only a few types of this group of diseases increase the risk of a severe course of SARS-CoV-2 infection. It is, for example, the most common symptomatic immunodeficiency disorder in adults (common variable immunodeficiency - CVID). Safety can be higher by taking preventive measures, such as vaccination against COVID-19, and also by using appropriate treatment of the disease. The main problem is that a large part of patients (in Europe - approximately 70-80%) still remain undiagnosed, and therefore now, even more attention should be paid to the alarm symptoms [27,28].

Conclusions

Primary immunodeficiencies constitute one of the challenges of current medicine. Deficit of knowledge about the immune system and immunodeficiency disease present in society and also difficulties in diagnosis cause that this disease is undetectable.

In effect, people suffer from numerous infections, experience medical complications, and are not treated. Also diagnosed immunodeficiencies significantly affect the lives of those affected.

The disease has an influence on their social contacts, job, frame of mind, and whole life. All these aspects caused the necessity of raising awareness about immunodeficiency, detectability of disease, and the possibility of minimizing adverse effects of this condition.

References

1. Tangye S.G., Al-Herz W., Bousfiha A., Chatila T., Cunningham-Rundles C., Etzioni A., Franco J.L., Holland S.M., Klein C., Morio T., Ochs H.D., Oksenhendler E., Picard

C., Puck J., Torgerson T.R., Casanova J.L., Sullivan K.E.: Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. Journal of Clinical Immunology, 2020, 40(1), 4-64.

2. Siedlar M., Pituch-Noworolska A., Szaflarska A., Kowalczyk D., Strojny W.: Pierwotne niedobory odporności. https://www.mp.pl/podrecznik/pediatria/chapter/B42.166.9 (cited 20.07.2021).
3. Picard C., Bobby Gaspar H., Al-Herz W., Bousfiha A., Casanova J.L., Chatila T., Crow Y.J., Cunningham-Rundles C., Etzioni A., Franco J.L., Holland S.M., Klein C., Morio T., Ochs H.D., Oksenhendler E., Puck J., Tang M.L.K., Tangye S.G., Torgerson T.R., Sullivan K.E.: International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. Journal of Clinical Immunology, 2018, 38(1), 96-128.
4. Bernatowska E., Pac M.: Polska Grupa Robocza ds. Pierwotnych Niedoborów Odporności - działania na rzecz wzrostu wykrywalności pierwotnych niedoborów odporności oraz dostępności leczenia substytucyjnego preparatami gammaglobulin dla pacjentów z niedoborami przeciwciał - raport z września 2013 roku. http://31.186.81.235:8080/api/files/view/50145.pdf (cited 20.07.2021).
5. Bousfiha A., Jeddane L., Picard C., Al-Herz W., Ailal F., Chatila T., Cunningham-Rundles C., Etzioni A., Franco J.L., Holland S.M., Klein C., Morio T., Ochs H.D., Oksenhendler E., Puck J., Torgerson T.R., Casanova J.L., Sullivan K.E., Tangye S.G.: Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. Journal of Clinical Immunology, 2020, 40(1), 66-81.
6. Jahnz-Różyk K., Siedlar M., Bernatowska E., Roliński J., Pac M., Więsik-Szewczyk E.: Primary immunodeficiencies – epidemiology, spending on therapy, diagnostic and therapeutic needs in Poland. https://www.jhpor.com/article/2080-primary-immunodeficiencies---epidemiology-spending-on-therapy-diagnostic-and-therapeutic-needs-in-poland (cited 20.07.2021).
7. Modell V., Knaus M., Modell F., Roifman C., Orange J., Notarangelo L.D.: Global overview of primary immunodeficiencies: a report from Jeffrey Modell Centers worldwide focused on diagnosis, treatment, and discovery. Journal of Immunology Research, 2014, 60(1), 132-44.

8. Selective IgA Deficiency. https://www.aaaai.org/Conditions-Treatments/Primary-Immunodeficiency-Disease/selective-iga-deficiency (cited 20.07.2021).
9. Pessach I., Walter J., Notarangelo L.D.: Recent advances in primary immunodeficiencies: identification of novel genetic defects and unanticipated phenotypes. Pediatric Research, 2009, 65, 3R-12R.
10. Ehlayel M., Bener A., Laban M.: Effects of family history and consanguinity in primary immunodeficiency diseases in children in Qatar. Open Journal of Immunology, 2013, 3, 47-53.
11. Arkwright P.D., Gennery A.R.: Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. Annals of the New York Academy of Sciences, 2011, 1238(1), 7–14.
12. Huissoon A.P., Krishna M.T.: Does this patient have an immunodeficiency? Clinical Medicine (London, England), 2011, 11(4), 380-4.
13. Locke B.A., Dasu T., Verbsky J.W.: Laboratory Diagnosis of Primary Immunodeficiencies. Clinical Reviews in Allergy & Immunology, 2014, 46(2), 154–168.
14. Pierwotne niedobory odporności u dorosłych. https://ipopi.org/wp-content/uploads/2018/11/dorosli_IPOPI.pdf?fbclid=IwAR00b01q4PeAxuAkFR32E8WYrBYiygdQqlP1K0EcPACeZqmp-GlFJK_w2F0 (cited 20.07.2021).
15. Pierwotne Niedobory Odporności - film dokumentalny. https://www.youtube.com/watch?v=Vu6bkhCZQf8 (cited 20.07.2021).
16. Gathmann B., Mahlaoui N., CEREDIH, Gérard L., Oksenhendler E., Warnatz K., Schulze I., Kindle G., Kuijpers T.W.; Dutch W.I.D., van Beem R.T., Guzman D., Workman S., Soler-Palacín P., De Gracia J., Witte T., Schmidt R.E., Litzman J., Hlavackova E., Thon V., Borte M., Borte S., Kumararatne D., Feighery C., Longhurst H., Helbert M., Szaflarska A., Sediva A., Belohradsky B.H., Jones A., Baumann U., Meyts I., Kutukculer N., Wågström P., Galal N.M., Roesler J., Farmaki E., Zinovieva N., Ciznar P., Papadopoulou-Alataki E., Bienemann K., Velbri S., Panahloo Z., Grimbacher B.: Clinical picture and treatment of 2212 patients with common variable immunodeficiency. The Journal of allergy and clinical immunology, 2014, 134(1), 116-26.

17. Hampson F.A., Chandra A., Screaton N.J., Condliffe A., Kumararatne D.S., Exley A.R., Babar J.L.: Respiratory disease in common variable immunodeficiency and other primary immunodeficiency disorders. Clinical Radiology, 2012, 67, 587–95.
18. Mozaffari H., Pourpak Z., Pourseyed S., Moin M., Farhoodi A., Aghamohammadi A., Movahedi M., Gharagozlou M., Entezari N.: Health-related quality of life in primary immune deficient patients. Iranian Journal of Allergy, Asthma and Immunology, 2006, 5, 23–7.
19. Kawalec,W.; Grenda R.; Kulus M.; Adamska E.; Choroby układu odpornościowego [w:] Pediatria II. Wydawnictwo Lekarskie PZWL, Warszawa, 2018, 899-916.
20. Fekrvand S., Yazdani R., Olbrich P., Gennery A., Rosenzweig S.D., Condino-Neto A., Azizi G., Rafiemanesh H., Hassanpour G., Rezaei N., Abolhassani H., Aghamohammadi A.: Primary Immunodeficiency Diseases and Bacillus Calmette-Guérin (BCG)-Vaccine-Derived Complications: A Systematic Review. The Journal of Allergy and Clinical Immunology: In Practice, 2020, 8(4), 1371-1386.
21. BCG vaccine. https://www.who.int/teams/health-product-and-policy-standards/standards -and- specifications/vaccines-quality/bcg (cited 20.07.2021).
22. Hesseling A.C., Rabie H., Marais B.J., Manders M., Lips M., Schaaf H.S., Gie R.P., Cotton M.F.,. van Helden P.D, Warren R.M., Beyers N.: Bacille Calmette-Guérin Vaccine—Induced Disease in HIV-Infected and HIV-Uninfected Children. Clinical Infectious Diseases, 2006, 42(4), 548–558.
23. Yamazaki-Nakashimada M.A., Unzueta A., Berenise Gámez-González L., González-Saldaña N., Sorensen R.U.: BCG: a vaccine with multiple faces. Hum Vaccin Immunother, 2020, 16(8), 1841-1850.
24. Sotomayor C.F., Palma J.B.: BCG vaccine administration schedule and primary immunodeficiencies: Is it time for a change? Revista chilena de pediatría, 2019, 90 (6), 668-674.
25. National Primary Immunodeficiency Resource Center. http://www.info4pi.org (cited 20.07.2021).
26. Eksperci: przebieg COVID-19 u chorych z pierwotnym niedoborem odporności jest podobny jak u pozostałych pacjentów. https://pulsmedycyny.pl/eksperci-przebieg-covid-19-u-chorych-z-pierwotnym-niedoborem-odpornosci-jest-podobny-jak-u-pozostalych-pacjentow-1114508 (cited 20.07.2021).

27. Przebieg COVID-19 u chorych z pierwotnym niedoborem odporności jest podobny jak u innych osób - strona 2. https://www.mp.pl/covid19/covid19-aktualnos ci/264944, przebieg-covid-19-u-chorych-z-pierwotnym-niedoborem-odpornosci-jest-podobny-jak - u-innych-osob,1 (cited 20.07.2021).

Recent advances in the pathogenesis and treatment of autosomal dominant polycystic kidney disease

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder with a prevalence of approximately 1/500 births worldwide [1]. Fluid-filled cysts are accumulated mainly in renal parenchyma. However, other organs, including the liver, pancreas, spleen, and even blood vessels, can be affected by polycystic liver disease and intracranial arterial aneurysms. Though cysts can originate from all kidney areas, they usually develop from the distal regions of nephrons and collecting ducts. These cysts may collect blood as the result of trauma but also can lead to a pyogenic infection and renal fibrosis. As the renal structure is being progressively disrupted over the years of chronic kidney disease, patients develop an end-stage renal disease associated with high mortality. Such a condition requires renal replacement therapy in nearly 50% of patients with ADPKD, as kidney failure develops in the fourth to sixth decade of life [2]. Therefore, over 10% of renal replacement therapies are due to the ADPKD [3]. In this paper, we submit an overview of the current ADPKD knowledge, focusing on the pathogenesis, diagnosis, and therapeutic possibilities.

Genes

For the majority of ADPKD cases, a mutation in either of two genes is responsible – PKD1 (polycystic kidney disease-1) or PKD2 (polycystic kidney disease-2), which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. ADPKD is a disease of enormous allelic heterogeneity, with most mutations resulting from nonsense, frameshift, or splice-site alterations. In the study of 400 families, 314 different truncating mutations to the PDK1 gene were found. And 91 truncating mutations in 166 families to PKD2 gene were described, with

aditional 25% of missense mutations [4]. Further, PKD1 and PDK2 mutations may have synergistic effects as in the family with bilinear inheritance, where one parent was diagnosed with PKD1 mutation. In contrast, in another with PKD2 mutation, children developed end-stage kidney disease (ESKD) approximately 20 years earlier than their relatives with only one PKD1/PKD2 mutation [5].

PDK1 gene (16p13.3) is responsible for over 80% ADPKD cases. This large gene is organized in 46 exons, encoding a large transcript characterized by an open reading frame (OTF) of 12,909 bp [6]. Exons 1-33 of PKD1 are located in a region that is duplicated six times in other locations on chromosome 16, making a molecular diagnostic and mutation search much more challenging [7]. PDK1 gene was found to have a high G.C. pairs content, multiple simple repeats, and 2.5-kb polypyrimidine tract within intron 21, which may interfere with replication, transcription, or RNA processing. Most mutations in the PKD1 gene produce truncated protein and are family-unique; however, missense mutations have been discovered [8]. PKD2 gene (4q22.1) is a smaller gene than PKD1, responsible for nearly 15% of ADPKD cases. Its structure is 25% homologous to a region of the PDK1 gene and is organized in 15 exons with an OTF of 2904 bp [9]. Patients with a mutation in the PKD2 gene compared to PKD1 patients show a later onset, have more prolonged renal survival, and present fewer complications [8].

The remaining 5-10% of cases are related to mutations in other loci or are yet genetically unsolved. These mutations, which may result in an ADPKD-like phenotype, may be located in hepatocyte nuclear factor 1β (HNF1B) – a transcription factor upregulating the expression of other PKD-associated genes, neutral α-glucosidase A.B. (GANAB) – responsible for protein folding, and DNAJB11 – encoding a chaperone protein associated with HSPA5 protein. In addition, mutations primarily connected to polycystic liver disease can also result in ADPKD-like disease, including SEC63 – encoding a protein required in endoplasmic reticulum protein translocation, and PRKCSH – encoding a regulatory β-subunit of glycosidase two required for protein folding [10].

PC-1 and PC-2 proteins

Polycystin-1 (PC-1) is an integral membrane protein containing 11 transmembrane domains, a large extracellular N-terminus domain, and a short cytoplasmic C-terminus tail responsible for regulating signaling cascades. PC-1 has a structure of a receptor or an adhesion

molecule [11]. Its expression has been observed in the epithelial cells of renal tubules, both developing and mature, as well as extrarenal tissues, including the heart, liver, bone, and endocrine glands. PC-1 levels are temporally regulated, reaching the highest levels in fetal renal tissue and low but detectable levels in adults. PC-1 proteins are mainly located in the cilium – an organelle arising from the surface of most cells, responsible for intercellular communication, but also in the lateral domain of plasma membrane and adhesion complexes in polarized epithelial cells [12]. PC-1 is cleaved in both N- and C-terminal domains. C-terminal cleavage at the G protein-coupled receptor proteolytic site (GPS) domain is thought to be important in the activation and regulation of the biosynthesis and trafficking of PC-1 [13]. This cleavage releases PC-1 fragments to the cytoplasm, which can subsequently migrate through the nuclear membrane and interact with the numerous nuclear signaling paths. Not all PC-1 proteins in the cell are cleaved, so full-length, and GPS-cleaved proteins coexist together.

Nevertheless, to be fully operational, PC-1 must undergo cleavage. Thus, cells with PC-1 unable to leave due to the mutation result in an ADPKD phenotype similar to the PC-1-null cells [14]. There is a coiled-coil domain at the C-terminal tail to interact non-covalently with PC-2 protein [8]. As a multifunctional protein localized subcellular to the plasma membrane and junctional complexes, the PC-1 role is suggested to be regulation in cell-cell and cell-matrix interactions. However, sensing fluid flow and pressure in the kidney may also be its function [15]. Therefore, mutations occurring in PC-1 may result in the impairment of intercellular communication and lead to pathological epithelial cell differentiation as well as numerous expressions of ADPKD [16].

Polycystin-2 (PC-2) protein is a nonselective cation channel with six transmembrane spanning domains and cytoplasmic N- and C-terminal domains. It is also known as TRPP2 (transient receptor potential polycystic 2); it is fought to be the third class of calcium release channels, beside TRPC1 and TRPV4, as it is insensitive to them as IP3 receptors and ryanodine receptors. It is permeable to Ca^{2+}, $Na^{+,}$ and K^{+} ions; however, only intracellular calcium level modulates PC-2 channel activity [17]. PC-2 is localized mainly in the endoplasmic reticulum and early Golgi but can also be found in the plasma membrane in complexes with PC-1 and primary cilium or mitotic spindles in tubules and collecting ducts of normal fetal and adult kidneys. PC-2 is a calcium-activated channel; its main function is to release Ca2+ ions from the intracellular stores if its local concentration grows [18]. However, in the polycystic complexes associated with the cell membrane, PC-2 is responsible for Ca^{2+} influx. This function is lost in

PC-1-null cells as the complex is impaired. Therefore, in ADPKD, intracellular calcium homeostasis is disrupted, resulting in decreased levels of Ca^{2+} and increased levels of cAMP [11].

PC-1 and PC-2 are suggested to interact in similar signaling cascades as clinical symptoms of their disruption are identical. These polycystins can function in a complex co-dependently and independently, varying from their location of subcellular compartments [19]. Especially in the primary cilium and endoplasmic reticulum, PC-1 and PC-2 interact through their C-terminal coiled domains, where PC-1 enhances binding to the GPS. At the same time, PC-2 decreases the ability of PC-1 to activate and cleave to the G protein [20]. Impairment in the function of one protein, either PC-1 or PC-2, negatively affects the other one. In ADPKD mutations of PC-1, which prevent GPS cleavage, a decrease in the level of both PC-1 and PC-2 has been noticed. Moreover, mutations in these proteins compromised, creating a functional ion channel associated with PC-2, due to the disrupted intrinsic function of the channel or complex formation [21].

Cyst formation

Cysts are small dilatations in the renal epithelium, which later grow into fluid-filled cavities of various sizes. Since in ADPKD patients, all of the cells carry germline mutations in one of the polycystin gene alleles, all these cells should be affected by cystogenesis. However, studies show that only a fraction (~1%) of nearly a million nephrons develop cysts during a patient's lifetime. To explain this phenomenon, a second-hit model has been proposed. According to this model, besides already existing germline mutation in either one of PKD1 or PKD2 alleles, a second normal allele must also acquire a somatic mutation, resulting in complete inactivation of PKD1 or PKD2 gene and thereby loss of polycystin function [22,23]. The kidney development stage when this second mutation occurs is of great importance to the disease severity. If gene knockout affects a developing kidney during its rapid cell differentiation, cystogenesis proceeds much faster than a mature kidney, where polycystin function is less critical. This may be due to the polycystins' role in nephrogenesis, which are crucial not for the nephron formation but the proper maintenance and subsequent elongation of the nephron segments [24]. However, further studies showed germline mutations (first-hit) and the second allele. Inactivation (second-hit) may not be enough to trigger cystogenesis,

and an additional factor is required; thus, a third-hit theory has been introduced. Cell ischemia and nephrotoxic injury are likely to induce rapid cyst growth, therefore accelerating ADPKD progression. In mice that underwent nephrectomy, the remaining kidney forced to compensate for the loss were observed to increase their glomerular filtration rate (GFR) and become hypertrophic, leading to a severe cystic kidney disease much sooner than the control group [25]. Also, cysts themselves can stimulate cyst formation as due to the cellular stress they induce on surrounding nephrons, the apoptosis of renal epithelium can be triggered [26].

As renal epithelium proliferates, the surface of the cyst lumen becomes more spherical. This may be due to the disruption in planar cell polarity, as cells divide more parallelly to the tubule rather than along its axis, thereby expanding the tubule instead of elongating it [27]. However, only loss of apical-basal polarity or planar cell polarity is not cytogenic itself, even though it defects the tubule diameter control; therefore, further models are required to be developed [28]. Secondly, cyst expansion is enhanced as the cyst fluid volume increases. This is due to the conversion of the cyst-lining cells from ion-absorptive to ion-secretory. Finally, transepithelial secretion is stimulated by cAMP and is dependent on the apical cystic fibrosis transmembrane regulator (CFTR). In ADPKD, disrupted PC-1 proteins can increase CFTR activity, upregulating Cl^- transport, resulting in fluid-filled cysts [29,30]. Moreover, the progressive activity of chemokines, cytokines, growth factors, interstitial fibroblasts, and macrophages induces inflammation and fibrosis. As new cysts are created and the disease proceeds, kidney fibrosis is developed, resulting in end-stage renal disease [2].

Diagnosis

When it comes to diagnosing patients suspected of ADPKD, the first tool used to screen out affected ones is ultrasound due to accessibility and non-invasive character of examination. A skilled radiologist can find cysts as small as 2 mm in diameter with the high-resolution ultrasound probe. The unified criteria for at-risk patients with PDK1 or PDK2 mutations are as follows: for patients aged 15 to 29, it is necessary to find at least three cysts, uni- or bilaterally; for ones aged 30 to 59 – at least two cysts bilaterally; and in older patients – at least four cysts bilaterally; while finding less than two in <40-year-old patients has been proved to be sufficient for disease exclusion [31]. In pediatric patients, strict criteria for Ultrasound was not precisely determined, and using ones for 15-year-old patients does not give enough sensitivity to depend

on them. However, at least one cyst in ultrasound imaging of kidney enlargement should concern practitioners to suspect ADPKD [32]. In MRI, considered more specific and sensitive, but also more expensive and sometimes involving sedation, there is required a presence of at least ten cysts in patients aged <40 years for confirmation, while the detection of fewer than five cysts excludes the disease [33,34]. Other forms of direct monitoring include blood pressure assessment and other symptoms such as back pain or dysuria [35]. Laboratory tests could also show impaired urinary concentration due to less reactivity to vasopressin, hyperfiltration, and restricted renal blood flow [36,37].

If the family history is negative (as it is for the quarter of patients with ADPKD), the imaging-based diagnosis must be extended by genetic testing. The same approach should be applied to potential kidney donors [38,39] and patients with preliminary radiological imaging results and prenatal diagnosis. However, in the latter, such diagnostics are rarely conducted [40]. Methods used for genetic testing are denaturing high-performance liquid chromatography (DHPLC), direct sequencing, targeted next-generation sequencing, or microarray, which can considerably shorten diagnosis time, as numerous variants of mutations are tested simultaneously [41-43].

There is also an ethical factor that is needed to be taken into consideration. Presymptomatic imaging and screening may bring a psychological burden to a patient and their parents, with the first manifestation occurring in adolescence or adulthood or possibly never giving any ailments other than imaging manifestation. Therefore, recommendations advise against the screening of asymptomatic patients born from affected parents [35].

Mutation in PDK1/2 genes can cause abnormalities in other organs, such as polycystic liver disease (PLD) being the most common, with prevalence, reported by Farooq et al. [44], of 12% affected by ADPKD, presenting abdominal pain, fever, jaundice, portal hypertension or ascites. Other locations of the cyst presence are the pancreas, seminal vesicles in men, arachnoid, and spinal meninges [45]. A complication that requires more attention is the formation of intracranial aneurysm (ICA), with prevalence ranging from 9% to 12% [35]. It is more common in patients with a family history of ICA. However, screening should be narrowed down to patients' previous aneurysm rupture, family history of aneurysm, subarachnoid hemorrhage, premature stroke, or family history of premature death [46]. Moreover, aortic and coronary arteries aneurysm, aortic dissections, aortic root dilatation, cerebral dolichoectasia, and mitral valve prolapse are other forms of cardiovascular complications [47].

Treatment

The current level of development in medicine allowed doctors to treat symptoms and complications and advance beyond that. All patients are encouraged to have a balanced diet, with a limited salt intake of up to 5 g/day [48]; having a high water intake; active lifestyle to keep body weight in optimal range; avoid alcohol, smoking, and usage of non-steroidal anti-inflammatory drugs [35,49]. Hypertension is usually treated using a single angiotensin-converting enzyme inhibitor, with target values of blood pressure of less than 110/75 mmHg in aged <50 years with preserved estimated glomerular filtration rate (eGFR) (≥60 mL/min/1,73m^2) without any other cardiovascular complications. Schrier et al. [50] have proven that strict control of blood pressure was more beneficial than the standard one (with the target set at 120/70-130/80 mmHg), bringing reduction in a left ventricular mass index, proteinuria, resistance in renal vessels, and perspective – slowing the decrease of eGFR.

Vasopressin V2 receptor antagonists first studied on rodent models were shown to reduce intracellular cAMP and, therefore, antiestrogenic [51]. Based on those studies, tolvaptan was introduced in the therapy of human ADPKD. A randomized controlled trial was conducted, in which 1445 patients with ADPKD were enrolled. The drug slowed total kidney volume increase (2,8%/year compared with 5,5%/year in the placebo group) [52]. Due to the lack of vasopressin effect on water retention, adverse effects included polydipsia, polyuria, nocturia, and an elevation of liver enzymes [53]. A follow-up study, scheduled in response to the U.S. Food and Drug Administration (FDA) uncertainty in the safety and efficacy, confirmed the previous findings, as patients' eGFR reduction has been slowed [54]. Currently, recommendations propose the usage of tolvaptan in the following patients: aged 18-55; with eGFR >25 ml/min/1,73m^2; at high risk (Mayo imaging classification 1C-1E or PROPKD score >6); with a history of decline in eGFR greater than 5 ml/min/1,73m^2 in one year. Main excluding factors from treatment involve pregnancy, lactation, uncorrected hypernatremia, history of liver injury, hypovolemia, inability to sense or respond to thirst, and urinary tract obstruction [55].

Due to their pleiotropic effects, Statins could be beneficial for maintaining the renal blood flow and reduce the inflammatory process in kidneys. In 2014 Cadnapaphornchai et al. [56] conducted a randomized trial on 110 children and adults with ADPKD, proving the effect of pravastatin, which considerably reduced the increase rate of total kidney volume (TKV, 23% vs. 31% placebo in 3 years; p=0.02). In contrast, Fassett et al. [57], in their study of 49 qualified

patients treated with 20 mg of pravastatin, have noticed no statistically significant difference in kidney function markers between drug and placebo receiving groups. Thus, two ongoing clinical trials are run to determine whether statins influence renal function [58,59].

mTOR pathway inhibitors, such as everolimus or sirolimus, were also considered, as the accelerated proliferation of epithelial cells is one of the mechanisms leading to the development of the cyst. However, clinical trials for those drugs have proven inefficient in slowing cyst growth rate [60,61]. Bosutinib, a tyrosine kinase inhibitor (TKI), seems to reduce the TKV growth rate without affecting eGFR [62]. Another TKI, tesevatinib underwent clinical trials to determine if TKI could be considered as a possible drug for ADPKD [63]. Somatostatin analogs in murine models inhibit cAMP synthesis, which translates to reduced proliferation of renal cells [64]. Thus, usage of, e.g., octreotide, long-acting synthetic somatostatin analog has been considered. A randomized, placebo-controlled, multicentre trial ALADIN tried to determine whether it could be used to treat patients, but without straightforward results. From year 1 to 3, mean eGFR and TKV were smaller in favor of a drug (89 vs. 78 ml/min/1,73m^2 and 1556.9 ml vs. 2161.2 ml respectively), but after the third year, changes in both eGFR and TKV were insignificant from the placebo group [65]. A follow-up study, ALADIN 2, aimed at patients in a later stage of kidney failure, confirmed the previous finding that octreotide could slow progress to end-stage renal disease (ESRD) [66]. Therefore, repurposing commonly used drugs, such as metformin, can be feasible. It is speculated that metformin can inhibit cyst formation through activation of the AMPK pathway, which was previously confirmed in the zebrafish model [67]. The ongoing trial is intended to confirm if that treatment is possible for humans [68], with stage 2 results showing a slight decrease in estimated GFR (-1.71 vs -3.07 ml/min/1.73m^2 for placebo), also highlighting that due to small patient group, a larger study is needed to define whether metformin therapy is effective [69].

The potential for disease management lies within gene therapy of the disease, but to this date, no clinical trials have been reported. Mice models proved that in some ADPKD Phenotypes restoring the function of altered genes brought positive changes on the cellular level [70]. However, further studies on a safe and efficient form of delivering genes are required [69].

Conclusions

Present advances in medicine allowed persons suffering from ADPKD to be found and

treated accordingly. Valuable advances were made in perceiving genetic and molecular causes of disease, resulting in an in-depth understanding of mechanisms leading to cyst development. At the same time, unified diagnosis tests hasten the process of deciding whether the person needs treatment. In addition, we can now use disease-modifying drugs instead of resorting only to symptomatic therapy. Further studies need to focus mainly on non-expensive methods of diagnosis, early markers, and possibly drugs targeting specifically altered fragments of genetic material.

References

1. Dalgaard O.Z., Nørby S.: Autosomal dominant polycystic kidney disease in the 1980's. Clinical genetics, 1989, 36(5), 320–325.
2. Grantham J.J.: Clinical practice. Autosomal dominant polycystic kidney disease. The New England journal of medicine, 2008, 359(14), 1477-1485.
3. Różański J., Ciechanowski K.: Autosomalnie dominująca wielotorbielowatość nerek. Fakty i mity. Forum Nefrologiczne, 2010, 3(3), 143-149.
4. Rossetti S., Consugar M.B., Chapman A.B., Torres V.E., Guay-Woodford L.M., Grantham J.J., Bennett W.M., Meyers C.M., Walker D.L., Bae K., Zhang Q.J., Thompson P.A., Miller J.P., Harris P.C.: CRISP Consortium: Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. Journal of the American Society of Nephrology, 2007, 18(7), 2143-60.
5. Pei Y., Paterson A.D., Wang K.R., He N., Hefferton D., Watnick T., Germino G.G., Parfrey P., Somlo S., St George-Hyslop P.: Bilineal disease and trans-heterozygotes in autosomal dominant polycystic kidney disease. American journal of human genetics, 2001, 68(2), 355–363.
6. The International Polycystic Kidney Disease Consortium: Polycystic kidney disease: the complete structure of the PKD1 gene and its protein. Cell, 1995, 81(2), 289–298.
7. Ong A.C., Harris P.C.: Molecular pathogenesis of ADPKD: the polycystin complex gets complex. Kidney international, 2005, 67(4), 1234–1247.
8. Ibraghimov-Beskrovnaya O., Bukanov N.: Polycystic kidney diseases: from molecular discoveries to targeted therapeutic strategies. Cellular and molecular life sciences, 2008, 65(4), 605–619.
9. Igarashi P., Somlo S.: Genetics and pathogenesis of polycystic kidney disease. Journal

of the American Society of Nephrology, 2002, 13(9), 2384–2398.

10. Bergmann C., Guay-Woodford L.M., Harris P.C., Horie S., Peters D.J.M., Torres V.E.: Polycystic kidney disease. Nature reviews. Disease primers, 2018, 4(1), 50.
11. Harris P.C., Torres V.E.: Polycystic kidney disease. Annual review of medicine, 2009, 60, 321–337.
12. Chapin H.C., Caplan M.J.: The cell biology of polycystic kidney disease. The Journal of cell biology, 2010, 191(4), 701–710.
13. Qian F., Boletta A., Bhunia A.K., Xu H., Liu L., Ahrabi A.K., Watnick T.J., Zhou F., Germino G.G.: Cleavage of polycystin-1 requires the receptor for egg jelly domain and is disrupted by human autosomal-dominant polycystic kidney disease 1-associated mutations. Proceedings of the National Academy of Sciences of the United States of America, 2002, 99(26), 16981–16986.
14. Xu Y., Streets A.J., Hounslow A.M., Tran U., Jean-Alphonse F., Needham A.J., Vilardaga J.P., Wessely O., Williamson M.P., Ong A.C.: The Polycystin-1, Lipoxygenase, and α-Toxin Domain Regulates Polycystin-1 Trafficking. Journal of the American Society of Nephrology, 2016, 27(4), 1159–1173.
15. Patel A., Honoré E.: Polycystins and renovascular mechanosensory transduction. Nature reviews. Nephrology, 2010, 6(9), 530–538.
16. Carone F.A., Nakamura S., Bacallao R., Nelson W.J., Khokha M., Kanwar Y.S.: Impaired tubulogenesis of cyst-derived cells from autosomal dominant polycystic kidneys. Kidney international, 1995, 47(3), 861–868.
17. Semmo M., Köttgen M., Hofherr A.: The TRPP subfamily and polycystin-1 proteins. Handbook of experimental pharmacology, 2014, 222, 675–711.
18. Koulen P., Cai Y., Geng L., Maeda Y., Nishimura S., Witzgall R., Ehrlich B.E., Somlo S.: Polycystin-2 is an intracellular calcium release channel. Nature cell biology, 2002, 4(3), 191–197.
19. Tsiokas L., Kim E., Arnould T., Sukhatme V.P., Walz G.: Homo- and heterodimeric interactions between the gene products of PKD1 and PKD2. Proceedings of the National Academy of Sciences of the United States of America, 1997, 94(13), 6965–6970.
20. Delmas P., Nomura H., Li X., Lakkis M., Luo Y., Segal Y., Fernández-Fernández J.M., Harris P., Frischauf A.M., Brown D.A., Zhou J.: Constitutive activation of G-proteins by polycystin-1 is antagonized by polycystin-2. The Journal of biological chemistry, 2002, 277(13), 11276–11283.

21. Giamarchi A., Padilla F., Coste B., Raoux M., Crest M., Honoré E., Delmas P.: The versatile nature of the calcium-permeable cation channel TRPP2. EMBO reports, 2006, 7(8), 787–793.
22. Qian F., Watnick T.J., Onuchic L.F., Germino G.G.: The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type I. Cell, 1996, 87(6), 979–987.
23. Harris P.C.: What is the role of somatic mutation in autosomal dominant polycystic kidney disease? Journal of the American Society of Nephrology, 2010, 21(7), 1073–1076.
24. Lantinga-van Leeuwen I.S., Leonhard W.N., van der Wal A., Breuning M.H., de Heer E., Peters D.J.: Kidney-specific inactivation of the Pkd1 gene induces rapid cyst formation in developing kidneys and a slow onset of disease in adult mice. Human molecular genetics, 2007, 16(24), 3188–3196.
25. Sharma N., Malarkey E.B., Berbari N.F., O'Connor A.K., Vanden Heuvel G.B., Mrug M., Yoder B.K.: Proximal tubule proliferation is insufficient to induce rapid cyst formation after cilia disruption. Journal of the American Society of Nephrology, 2013, 24(3), 456–464.
26. Leonhard W.N., Zandbergen M., Veraar K., van den Berg S., van der Weerd L., Breuning M., de Heer E., Peters D.J.: Scattered Deletion of PKD1 in Kidneys Causes a Cystic Snowball Effect and Recapitulates Polycystic Kidney Disease. Journal of the American Society of Nephrology, 2015, 26(6), 1322–1333.
27. Fischer E., Legue E., Doyen A., Nato F., Nicolas J.F., Torres V., Yaniv M., Pontoglio M.: Defective planar cell polarity in polycystic kidney disease. Nature genetics, 2006, 38(1), 21–23.
28. Kunimoto K., Bayly R.D., Vladar E.K., Vonderfecht T., Gallagher A.R., Axelrod J.D.: Disruption of Core Planar Cell Polarity Signaling Regulates Renal Tubule Morphogenesis but Is Not Cystogenic. Current biology, 2017, 27(20), 3120–3131.e4.
29. Grantham J.J.: The etiology, pathogenesis, and treatment of autosomal dominant polycystic kidney disease: recent advances. American journal of kidney diseases: the official journal of the National Kidney Foundation, 1996, 28(6), 788–803.
30. Ikeda M., Fong P., Cheng J., Boletta A., Qian F., Zhang X.M., Cai H., Germino G.G., Guggino W.B.: A regulatory role of polycystin-1 on cystic fibrosis transmembrane conductance regulator plasma membrane expression. Cellular physiology and

biochemistry: international journal of experimental cellular physiology, biochemistry, and pharmacology, 2006, 18(1-3), 9–20.

31. Pei Y., Obaji J., Dupuis A., Paterson A.D., Magistroni R., Dicks E., Parfrey P., Cramer B., Coto E., Torra R., San Millan J.L., Gibson R., Breuning M., Peters D., Ravine D.: Unified criteria for ultrasonographic diagnosis of ADPKD. Journal of the American Society of Nephrology, 2009, 20(1), 205–212.
32. Gimpel C., Avni E.F., Breysem L., Burgmaier K., Caroli A., Cetiner M., Haffner D., Hartung E.A., Franke D., König J., Liebau M.C., Mekahli D., Ong A.C.M., Pape L., Titieni A., Torra R., Winyard P.J.D., Schaefer F.: Imaging of Kidney Cysts and Cystic Kidney Diseases in Children: An International Working Group Consensus Statement. Radiology, 2019, 290(3), 769–782.
33. Pei Y., Hwang Y.H., Conklin J., Sundsbak J.L., Heyer C.M., Chan W., Wang K., He N., Rattansingh A., Atri M., Harris P.C., Haider M.A.: Imaging-based diagnosis of autosomal dominant polycystic kidney disease. Journal of the American Society of Nephrology, 2015, 26(3), 746–753.
34. Cadnapaphornchai M.A., Masoumi A., Strain J.D., McFann K., Schrier R.W.: Magnetic resonance imaging of kidney and cyst volume in children with ADPKD. Clinical journal of the American Society of Nephrology, 2011, 6(2), 369–376.
35. Chapman A.B., Devuyst O., Eckardt K.U., Gansevoort R.T., Harris T., Horie S., Kasiske B.L., Odland D., Pei Y., Perrone R.D., Pirson Y., Schrier R.W., Torra R., Torres V.E., Watnick T., Wheeler D.C.: Conference Participants: Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney international, 2015, 88(1), 17–27.
36. Torres V.E.: Water for ADPKD? Probably, yes. Journal of the American Society of Nephrology, 2006, 17(8), 2089–2091.
37. Chapman A.B., Johnson A., Gabow P.A., Schrier R.W.: The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. The New England Journal of Medicine, 1990, 323(16), 1091–1096.
38. Iliuta I.A., Kalatharan V., Wang K., Cornec-Le Gall E., Conklin J., Pourafkari M., Ting R., Chen C., Borgo A.C., He N., Song X., Heyer C.M., Senum S.R., Hwang Y.H., Paterson A.D., Harris P.C., Khalili K., Pei Y.: Polycystic Kidney Disease without an

39. Apparent Family History. Journal of the American Society of Nephrology, 2017, 28(9), 2768–2776.
40. Kanaan N., Devuyst O., Pirson Y.: Renal transplantation in autosomal dominant polycystic kidney disease. Nature reviews. Nephrology, 2014, 10(8), 455–465.
41. De Rycke M., Georgiou I., Sermon K., Lissens W., Henderix P., Joris H., Platteau P., Van Steirteghem A., Liebaers I.: PGD for autosomal dominant polycystic kidney disease type 1. Molecular human reproduction, 2005, 11(1), 65–71.
42. Rossetti S., Strmecki L., Gamble V., Burton S., Sneddon V., Peral B., Roy S., Bakkaloglu A., Komel R., Winearls C.G., Harris P.C.: Mutation analysis of the entire PKD1 gene: genetic and diagnostic implications. American journal of human genetics, 2001, 68(1), 46–63.
43. Husson H., Manavalan P., Akmaev V.R., Russo R.J., Cook B., Richards B., Barberio D., Liu D., Cao X., Landes G.M., Wang C.J., Roberts B.L., Klinger K.W., Grubman S.A., Jefferson D.M., Ibraghimov-Beskrovnaya O.: New insights into ADPKD molecular pathways using combination of SAGE and microarray technologies. Genomics, 2004, 84(3), 497–510.
44. Bullich G., Domingo-Gallego A., Vargas I., Ruiz P., Lorente-Grandoso L., Furlano M., Fraga G., Madrid Á., Ariceta G., Borregán M., Piñero-Fernández J.A., Rodríguez-Peña L., Ballesta-Martínez M.J., Llano-Rivas I., Meñica M.A., Ballarín J., Torrents D., Torra R., Ars E.: A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases. Kidney international, 2018, 94(2), 363–371.
45. Farooq Z., Behzadi A.H., Blumenfeld J.D., Zhao Y., Prince M.R.: Complex liver cysts in Autosomal Dominant Polycystic Kidney Disease. Clinical imaging, 2017, 46, 98–101.
46. Pirson Y.: Extrarenal manifestations of autosomal dominant polycystic kidney disease. Advances in chronic kidney disease, 2010, 17(2), 173–180.
47. Zhou Z., Xu Y., Delcourt C., Shan J., Li Q., Xu J., Hackett M.L.: Is Regular Screening for Intracranial Aneurysm Necessary in Patients with Autosomal Dominant Polycystic Kidney Disease? A Systematic Review and Meta-analysis. Cerebrovascular diseases (Basel, Switzerland), 2017, 44(1-2), 75–82.
48. Perrone R.D., Malek A.M., Watnick T.: Vascular complications in autosomal dominant

polycystic kidney disease. Nature reviews. Nephrology, 2015, 11(10), 589–598.

49. Soroka S., Alam A., Bevilacqua M., Girard L.P., Komenda P., Loertscher R., McFarlane P., Pandeya S., Tam P., Bichet D.G.: Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease. Canadian journal of kidney health and disease, 2018, 5, 2054358118801589.
50. Chebib F.T., Torres V.E.: Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease. Clinical journal of the American Society of Nephrology, 2018, 13(11), 1765–1776.
51. Schrier R.W., Abebe K.Z., Perrone R.D., Torres V.E., Braun W.E., Steinman T.I., Winklhofer F.T., Brosnahan G., Czarnecki P.G., Hogan M.C., Miskulin D.C., Rahbari-Oskoui F.F., Grantham J.J., Harris P.C., Flessner M.F., Bae K.T., Moore C.G., Chapman A.B., HALT-PKD Trial Investigators: Blood pressure in early autosomal dominant polycystic kidney disease. The New England journal of medicine, 2014, 371(24), 2255–2266.
52. Wang X., Wu Y., Ward C.J., Harris P.C., Torres V.E.: Vasopressin directly regulates cyst growth in polycystic kidney disease. Journal of the American Society of Nephrology, 19(1), 102–108.
53. Torres V.E., Chapman A.B., Devuyst O., Gansevoort R.T., Grantham J.J., Higashihara E., Perrone R.D., Krasa H.B., Ouyang J., Czerwiec F.S., TEMPO 3:4 Trial Investigators: Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England Journal of Medicine, 2012, 367(25), 2407–2418.
54. Devuyst O., Chapman A.B., Shoaf S.E., Czerwiec F.S., Blais J.D.: Tolerability of Aquaretic-Related Symptoms Following Tolvaptan for Autosomal Dominant Polycystic Kidney Disease: Results From TEMPO 3:4. Kidney international reports, 2017, 2(6), 1132–1140.
55. Torres V.E., Chapman A.B., Devuyst O., Gansevoort R.T., Perrone R.D., Koch G., Ouyang J., McQuade R.D., Blais J.D., Czerwiec F.S., Sergeyeva O., REPRISE Trial Investigators: Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. The New England journal of medicine, 2017, 377(20), 1930–1942.
56. Chebib F.T., Perrone R.D., Chapman A.B., Dahl N.K., Harris P.C., Mrug M., Mustafa R.A., Rastogi A., Watnick T., Yu A.S.L., Torres V.E.: A Practical Guide for Treatment

of Rapidly Progressive ADPKD with Tolvaptan. Journal of the American Society of Nephrology, 2018, 29(10), 2458–2470.

57. Cadnapaphornchai M.A., George D.M., McFann K., Wang W., Gitomer B., Strain J.D., Schrier R.W.: Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. Clinical journal of the American Society of Nephrology, 2014, 9(5), 889–896.
58. Fassett R.G., Coombes J.S., Packham D., Fairley K.F., Kincaid-Smith P.: Effect of pravastatin on kidney function and urinary protein excretion in autosomal dominant polycystic kidney disease. Scandinavian journal of urology and nephrology, 2010, 44(1), 56–61.
59. Pastor-Soler N.M., University of Southern California: Pravastatin and Alkali Therapy in Patients With Autosomal Dominant Polycystic Kidney Disease (ADPKD-SAT). https://clinicaltrials.gov/ct2/show/NCT04284657?term=statin&cond=ADPKD&draw=2&rank=3 (cited 22.07.2021).
60. University of Colorado: Statin Therapy in Patients With Early Stage ADPKD. https://clinicaltrials.gov/ct2/show/NCT03273413?term=statin&cond=ADPKD&draw=2&rank=1 (cited 22.07.2021).
61. Serra A.L., Poster D., Kistler A.D., Krauer F., Raina S., Young J., Rentsch K.M., Spanaus K.S., Senn O., Kristanto P., Scheffel H., Weishaupt D., Wüthrich R.P.: Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. The New England journal of medicine, 2010, 363(9), 820–829.
62. Walz G., Budde K., Mannaa M., Nürnberger J., Wanner C., Sommerer C., Kunzendorf U., Banas B., Hörl W.H., Obermüller N., Arns W., Pavenstädt H., Gaedeke J., Büchert M., May C., Gschaidmeier H., Kramer S., Eckardt K.U.: Everolimus in patients with autosomal dominant polycystic kidney disease. The New England journal of medicine, 2010, 363(9), 830–840.
63. Tesar V., Ciechanowski K., Pei Y., Barash I., Shannon M., Li R., Williams J.H., Levisetti M., Arkin S., Serra A.: Bosutinib versus Placebo for Autosomal Dominant Polycystic Kidney Disease. Journal of the American Society of Nephrology, 2017, 28(11), 3404–3413.
64. Kadmon Corporation LLC: Study of the Efficacy and Safety of Tesevatinib in Subjects With ADPKD. https://clinicaltrials.gov/ct2/show/NCT03203642 (data pobrania: 22.07.2021).

65. Torres V.E., Harris P.C.: Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. Journal of the American Society of Nephrology, 2014, 25(1), 18–32.
66. Caroli A., Perico N., Perna A., Antiga L., Brambilla P., Pisani A., Visciano B., Imbriaco M., Messa P., Cerutti R., Dugo M., Cancian L., Buongiorno E., De Pascalis A., Gaspari F., Carrara F., Rubis N., Prandini S., Remuzzi A., Remuzzi G., Ruggenenti P., ALADIN study group: Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomized, placebo-controlled, multicenter trial. Lancet, 2013, 382(9903), 1485–1495.
67. Perico N., Ruggenenti P., Perna A., Caroli A., Trillini M., Sironi S., Pisani A., Riccio E., Imbriaco M., Dugo M., Morana G., Granata A., Figuera M., Gaspari F., Carrara F., Rubis N., Villa A., Gamba S., Prandini S., Cortinovis M., Remuzzi A., Remuzzi G., ALADIN 2 Study Group: Octreotide-LAR in later-stage autosomal dominant polycystic kidney disease (ALADIN 2): A randomized, double-blind, placebo-controlled, multicenter trial. PLoS medicine, 2019, 16(4), e1002777.
68. Chang M.Y., Ma T.L., Hung C.C., Tian Y.C., Chen Y.C., Yang C.W., Cheng Y.C.: Metformin Inhibits Cyst Formation in a Zebrafish Model of Polycystin-2 Deficiency. Scientific reports, 2017, 7(1), 7161.
69. Bae K.T., Tufts Medical Center, University of Maryland, University of Southern California, United States Department of Defense: Metformin as a Novel Therapy for Autosomal Dominant Polycystic Kidney Disease (TAME). https://clinicaltrials.gov/ct2/show/NCT02656017 (cited 22.07.2021).
70. Perrone R.D., Abebe K.Z., Watnick T., Althouse A., Hallows K.R., Lalama C.M., Miskulin D.C., Seliger S.L., Tao C., Harris P.C., Bae K.T.: Primary results of the randomized trial of metformin administration in polycystic kidney disease (TAME PKD). Kidney international, 2021, S0085-2538(21)00601-3.
71. Li A., Tian X., Zhang X., Huang S., Ma Y., Wu D., Moeckel G., Somlo S., Wu G.: Human polycystin-2 transgene dose-dependently rescues ADPKD phenotypes in Pkd2 mutant mice. The American journal of pathology, 2015, 185(10), 2843–2860.

Current treatment strategies for localized scleroderma

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Introduction

Localized scleroderma (L.S.), also known as morphea is a rheumatoid autoimmune disease of the skin and subcutaneous tissues. Its prevalence is estimated to be 0.4-2.7 per 100 000 patients [1,2]. The exact etiology remains unknown. However, some factors impact L.S. development, such as: genetics, immune factors, trauma, and drugs (for example, bisoprolol, bleomycin, peplomycin, D-penicillamine, bromocriptine, L-5-hydroxytryptophan, and the combination of carbidopa with pentazocine and balicatib) [3,4].

Lesions in morphea are thought to be initiated by vascular injury, which leads to the increased expression of adhesion molecules stimulating the inflammation cells. The inflammation raises profibrotic cytokines such as transforming growth factor-beta, which increase collagen synthesis (especially subtype I and III) and inhibit its destruction [5]. This process results in fibrosis as well as sclerosis of the skin and subcutaneous tissues. In more severe cases, tissue atrophy occurs [6].

Localized scleroderma can be differentiated from systemic sclerosis by lacking specific symptoms such as sclerodactyly, Raynaud sign and nail fold capillary changes [5]. Morphea can be divided into several subtypes, each characterized by the shape and involvement of the diverse lesion of different tissues, such as skin, adipose tissue, muscle, and bone [7].

The most common subtypes are listed in table 1. Less frequent morphea subtypes include *morphea guttata*, nodular morphea, Parry-Romberg syndrome or progressive facial hemiatrophy, eosinophilic fasciitis, Shulman syndrome, and *lichen sclerosus et atrophicus* [2].

The diagnosis is based on clinical features as well as histopathological examination and laboratory testing. There are no antibodies specific to morphea; however, ANA antibodies, anti-histone antibodies and SS-DNA antibodies appear in some patients. Some studies showed 30% of patients with morphea do acquire positive ANA antibodies [9]. Moreover, patients present

positive eosinophilia and inflammation markers. In more serious cases, magnetic resonance imaging is necessary to estimate the severity of lesions [10].

Table 1. Morphea classification based on European Society of Pediatric Rheumatology criteria [8]

Subtype	Subclass	Clinical features
Circumscribed or plaque morphea	Superficial	• Round or oval lesions limited to dermis and epidermis • Sometimes inflammation around plaques • Mostly on trunk • The tendency to the self-healing
	Deep	• Oval lesions which indurate deeper in the skin (subcutaneous tissues, fascia, and muscles)
Linear morphea	Trunk or limbs	• Linear lesions on extremities • Include dermis, subcutaneous tissue, muscles, and bones
	Head	• Linear lesions on the head • Include dermis and bones
Generalized morphea		• 4 or more plaques at least 3 cm each in 2 or more anatomical sides
Pansclerotic morphea		• The most severe subtype • Circumferential lesion on most of the body • Include dermis, subcutaneous tissue, muscles, and bones
Mixed morphea		• Combination of any of previous subtypes

Patients suffering from localized scleroderma are more prone to other autoimmune diseases such as lupus erythematosus, plaque psoriasis, multiple sclerosis, vitiligo, Hashimoto disease, diabetes mellitus, rheumatoid arthritis, and alopecia areata [7].

In this paper, we present the current treatment for localized scleroderma based on the most present guidelines. Reviewing the therapy, we focused on clinical indications, possible usage schemes, and potential adverse effects. The current treatment include topical agents (imiquimod, tacrolimus, calcipotriol, calcipotriol/betamethasone dipropionate and calcipotriol) systemic (steroids, methotrexate, and mycophenolate mofetil) and phototherapy [1].

Calcineurin inhibitors

Tacrolimus is known to be the most effective topical agent. Studies showed the

effectiveness of 0.1% topical tacrolimus, applied two times a day, for 12 months [11]. Tacrolimus administered on the skin for four months decreased early erythematous lesions and no recurrence or adverse effects were noticed [12].

Another study revealed complete remission of early and late lesions during tacrolimus therapy. The ointment was applied twice a day at night under the occlusion [13]. Further, tacrolimus showed a major effect in the treatment of superficial plaque morphea [14].

Besides tacrolimus' efficiency against many localized scleroderma subtypes, it is recommended the most frequently to treat active localized plaques [15].

Topical corticosteroids

Although topical corticosteroids are the most commonly used in morphea treatment, current literature does not show their effectiveness in monotherapy. The study from 2014 indicated the lesions' remission was achieved by combining betamethasone dipropionate with calcipotriol [16].

Despite the lack of data, some recommendations consider the use of medium and high potency topical corticosteroids to treat the active phase of plaque morphea [17]. The topical corticosteroid therapy's main aim is to reduce inflammation, which could subsequently lead to the tissue's sclerotization [18].

Vitamin D analogues

Vitamin D analogues are the next agents which can be potentially used in the L.S. therapy. The study conducted on 12 patients resistant to the previous treatment showed the efficacy of 0.005% calcipotriol after 3 months of the therapy. The ointment was applied twice a day under the occlusion. There were no relevant side effects noticed [19]. Few case-report studies confirmed the effectiveness of vitamin D analogues in monotherapy as well as in combination with corticosteroids [20-22].

The study carried out on 19 patients under 18 years of age demonstrated that the calcipotriol combined with low dosages of phototherapy (ultraviolet A1) has a positive impact on lesions reduction [23].

Furthermore, studies indicated that calcipotriol with P.U.V.A. (70J/cm2) is efficient for the linear scleroderma [24].

Topical imiquimod

Imiquimod is the immune-modulating agent stimulating the secretion of inhibitory cytokines, such as IFN-alfa or IFN-gamma, which suppress collagen production. Studies showed the effectiveness of 5% imiquimod administered once a day for five following days for four months. The complete remission was noted in 2 patients, and partial remission was observed in 12 people suffering from morphea [25,26]. Prospective studies revealed the efficiency of imiquimod in the pediatric population, especially in plaque morphea [27]. In adults, imiquimod is recommended in residual sclerosis in the plaque subtype and the linear subtype affecting limbs and head [17].

Systemic corticosteroids

Systemic corticosteroids (S.C.S.) are used in the early stages of morphea, in the induction phase, as other drugs such as methotrexate need a few months to achieve the therapeutic effect. The dosage of oral corticosteroids is 0.5-1mg/kg/day for 3 months, while intravenous methylprednisolone (IVMP) – 30mg/kg/day for 3 days every month for 3 months [2]. In the study conducted on 17 patients who suffered from morphea, prednisone was administered for 5-70 months. In all patients, the remission of lesions has been observed. Unfortunately, in 6 patients (35%) after the therapy, a recurrence has been noticed [28]. In the next retrospective study, the medical history of 28 patients was analyzed. All these patients received prednisone for 3-39 months. In 24 subjects, the remission was satisfying; however, in 9 out of 20 patients (45%), who did not use any other treatment, a recurrence was observed [29]. The side effects of systemic corticosteroids include acne, hirsutism, a gain of weight, glaucoma, growth inhibition in children, osteoporosis, opportunistic infections, hypertension, Cushing's syndrome, and diabetes [30-32]. Nevertheless, there are not many studies concerning corticosteroids in monotherapy. In most of the literature, corticosteroids are combined with methotrexate [2].

Methotrexate

Methotrexate (MTX) is considered, alongside S.C.S. therapy, as an effective and safe substance both in juvenile and adult patients. The most prominent double-blind, randomized

trial conducted by Zulian et al. [33] consisted of 70 patients, 48 of whom were treated with MTX dosed 15 mg/m^2/week, max. 20 mg/m^2/week, and the therapy was continued for 12 months after acceptable results were achieved. Additionally, all patients received oral prednisone in 1 mg/kg/day dose, max. 50 mg/kg/day for the first three months of study. Overall results showed an improvement in MTX-treated patients, with a worsening in the placebo group. Koch et al. [34], using the same protocol for linear morphea came to the similar conclusion, as seven patients required a second course, and 1 out of 17 subjects qualified for research required a third course of MTX to achieve remission. Another form of "bridging treatment" is using I.V.M.P. pulses. In one study, pediatric patients were administered 0.3 to 0.6 mg/kg/week of MTX alongside IVMP (30 mg/kg) for 3 days monthly for 3 months [35]. In the other study, adult patients were treated with an MTX dose of 15 mg/week, combined with pulsed I.V.M.P. (1000 mg for 3 days monthly) for at least 6 months [36]. Both of them resulted in successful disease management. A single therapy of solely MTX was also considered successful, with an improvement after the 24th week of the study, measured with modified skin score (M.S.S.) and visual analogue scale (VAS) [37]. MTX therapy is considered to be well-tolerated, with mild adverse effects including nausea, headache, fatigue, and hepatotoxicity [33,38]. Supplementation of folic acid can reduce adverse effects and increase the total treatment success rate [39]. In summary, MTX is recommended in systemic morphea therapy, but several elements are still needed to be taken into consideration, such as the usage of single MTX, MTX with oral steroids, or MTX with intravenous steroid pulses. Other ones are the dosage of the steroids above or whether to introduce MTX early, alongside topical treatment. Therefore, further randomized trials are necessary.

Mycophenolate

If MTX seems ineffective in disease management or a patient does not tolerate MTX, another antirheumatic drug, mycophenolate mofetil (MMF) can be introduced. Martini et al. [40] carried out the study where ten juvenile patients, previously treated with MTX and S.C.S., showed little to no progress and underwent MMF therapy receiving 600 to 1200 mg/m^2/day twice daily. In six patients, MMF has been combined with MTX. Results showed a response to MMF, and no more new lesions were present during the study. In 9 patients, there was a skin softening, in 7 – the disappearance of erythema, and in 3 – an improvement of the restriction of joint movement. Only one patient complained about abdominal discomfort. Other studies, in

which seven patients participated, were receiving 500 to 2500 mg of MMF, showed remission in 4 patients, which was maintained in one. Unfortunately, one patient developed elevated liver enzymes, which resulted in a withdrawal from the study [41]. More trials are needed to determine whether MMF is safe and effective in the management of morphea.

Phototherapy

Due to the recent advances in photo dermatology, phototherapy has emerged as one of the well-studied therapeutic methods of localized scleroderma. Using the ultraviolet radiation sources electromagnetic beams of a specific wavelength can be applied to the skin. The electromagnetic spectrum of ultraviolet can be divided into three ranges, including ultraviolet C (U.V.C., 200-290 nm), ultraviolet B (UVB, 290-320 nm), and ultraviolet A (UVA, 320-400 nm), which can be further subdivided into UVA1 (340–400 nm) and UVA2 (320–340 nm). However, currently applied phototherapeutic modalities include broadband ultraviolet B (UVB 290–320 nm), narrowband UVB (311–313 nm), ultraviolet A, ultraviolet A1, psoralen and UVA (P.U.V.A.), and extracorporeal photochemotherapy [42]. The longer wavelengths, such as UVA, are able to penetrate deeper into the skin, and therefore, cause less sunburn adverse effects. On the contrary, shorter wavelengths like UVB transmit their energy mostly to the upper dermis, thus resulting in increased sunburn. Therefore, as UVA penetrates deeper it has been a target for studies over localized scleroderma treatment. UVA radiation affects fibroblasts, dendritic cells, vascular epithelium, and inflammatory cells, leading to the lymphocyte apoptosis, cytokine alteration, and collagen synthesis inhibition. Nevertheless, in L.S. subtypes involving deeper skin structures, such as fat tissue, muscles, or bones, it may not be effective enough [43].

Psoralen and UVA irradiation (P.U.V.A.) apply oral, topical, or bath psoralen followed by exposure to UVA radiation in phototherapy or direct sunlight (PUVAsol). Presently used psoralens include methoxsalen or 8-methoxy psoralen, which enter the cells and intercalate between D.N.A. base pairs. Psoralens require high-intensity UVA radiation to activate, and by absorbing photons, they can covalently bind to the D.N.A. and form crosslinks [44]. In P.U.V.A. therapy reactive oxygen species are generated as well, resulting in cell membrane damage [45].

P.U.V.A. has been proved to activate metalloproteinase 1 (collagenase 1, MMP-1), important for collagen renewal [46]. Moreover, P.U.V.A. leads to the apoptosis of T-cells and

reduces serum V.C.A.M. levels, however, it increases TNF-α levels. In bath-PUVA a reduction of hydroxylysylpyridinoline and lysylpyridinoline in skin samples has been observed [47]. European Dermatology Forum S1 guidelines by Knobler et al. [8] recommend using bath-PUVA rather than oral administration of psoralens to avoid side effects. Performed 2–3 times weekly for a total of 30 irradiations, P.U.V.A. can result in a satisfactory skin lesions reduction in L.S. patients. A study of Pavlotsky et al. [48] shows that P.U.V.A. can be an effective and well-tolerated first-line treatment of L.S. Complete remission has been achieved in 39% of subjects using a mean cumulative dose of 115 J/cm^2, and a clinical improvement (softening and regression) has been observed in 50% of subjects. Bath-PUVA is recommended for the late stage of localized scleroderma when sclerosis predominates over inflammation [30]. In a study by Grundmann-Kollmann et al. [49] cream-PUVA has been suggested to be a potential alternative to bath-PUVA, as a significant clinical improvement or clearance has been achieved in all subjects; however, this study included only four patients. Thence, P.U.V.A. leads to antiproliferative, antiangiogenic, apoptotic, and immunosuppressive effects in the upper and middle reticular dermis layers [50].

In the early stages of localized scleroderma, UVA1 therapy can be more beneficial when an inflammation predominates sclerotic changes. UVA1 comprise three different dosages, including low-dose UVA1 (10–29 J/cm²), medium-dose UVA1 (30–59 J/cm²), and high-dose UVA1 (60–130 J/cm²) [8]. UVA1 radiation enhances a metalloproteinase-1 (MMP-1) gene expression, increasing dermal fibroblasts' synthesis. Due to the MMP-1 activity, as fibrillar collagens type I and III are hydrolyzed. Therefore, collagen structures become less dense and smother in comparison to non-UVA1 patients [51]. Further, UVA1 reduces decorin (a proteoglycan influencing fibrinogenesis) levels in the upper to mid-dermis [52]. Furthermore, studies show UVA1 can decrease TGF-β1 levels in fibroblast, resulting in an antifibrotic effect [53]. Moreover, UVA1 induces significant immunomodulatory effects in L.S. patients, leading to the T-cells apoptosis [54]. UVA1 downregulates interleukin-6 (IL-6) and IL-8 production. It also induces an MMP-1 expression by IL-1 and IL-6-related paths [55]. An increased level of TNFα has also been observed, leading to reduced collagen I and III production due to the inhibition of collagen mRNA and fibronectin as well as enhancement of collagenase expression [56]. Similar to P.U.V.A., UVA1 irradiation generates reactive oxygen species, by inducing heme oxygenase-1 in fibroblasts [57]. In European Dermatology Forum S1 guidelines consensus approves either low, medium, or high dose UVA1 to be used in treating L.S. However, high dose UVA1 seems to have higher effectiveness. The UVA1 course consists of

at least 30 irradiations performed 3-5 times in a week [8]. Nevertheless, in nearly 50% of patients undergoing UVA1 therapy, a recurrence within three years has been observed [58]. These patients may benefit from a second UVA1 course [8]. In a study by Kreuter et al. [59], a narrowband UVB (NB-UVB, 310-315 nm, peak at 311 nm) has been used to treat localized scleroderma. The irradiation of 18 subjects five times weekly for eight weeks resulted in a significant reduction of the clinical score from baseline to the end of the treatment. Thus, Narrowband UVB has started to be considered an effective therapeutic option, as it was the first trial including NB-UVB in the L.S. therapy. However, medium-dose UVA1 phototherapy occurred to be significantly more effective than narrowband UVB.

Other therapies

Hydroxychloroquine and cyclosporine are also considered possible drugs. The response to the treatment was observed in 78 out of 84 (93%) patients for hydroxychloroquine [60], and 11 out of 12 (92%) for cyclosporine [61]. However, with potential side effects and a lack of in-depth research, those drugs are not listed in recommendations [62].

Potential biological treatment comprises anti-IL6 humanized monoclonal antibody tocilizumab [63] and sarilumab, which are evaluated now [64]. Others include abatacept, CTLA-4 fusion protein [65], mTOR inhibitors tacrolimus [66] and everolimus [67], tyrosine kinase inhibitor imatinib [68,69], though those studies were only cased reports and non-randomized studies. Anti-TNF-alpha agents, like rituximab and infliximab, should be used with caution, as their usage may potentially induce morphea [70,71].

Physiotherapy, alongside medication, can improve mobility, restore movement range, and help maintain muscle strength [7], while surgical reconstruction, such as fat grafting, can be beneficial with patients with dysmorphia [72]. Orthopedic complications, such as limb length discrepancy or limb atrophy, surgical treatment of those above are to be considered as well [73].

Treatment regimens

In the treatment of L.S., various therapeutic methods are combined in several regimens in order to match patients individually depending on their predispositions and contraindications. Furthermore, the chosen regimen depends on the L.S. subtype as skin-limited subtypes may require only superficial treatment, whereas a systemic treatment may be necessary for deeper

tissue involvement. The recommendations presented below are based on European Dermatology Forum S1 guidelines by Knobler et al. [8].

For patients affected by superficial-ranged subtypes of L.S. involving the dermis only, topical therapy is recommended as a first-line treatment. Regimens, listed in table 2, include topical glucocorticoids, which should not be applied for longer than 3 months as they may induce potential severe adverse effects. In such a case, interval therapy should be considered. Glucocorticoids are advised in the active phase of L.S., as they are not effective in the sclerotic phase. Further, UVA-1 is suggested to be administered in pulse courses and in low doses [74].

Table 2. Treatment of L.S. subtypes with limited skin involvement [8,74]

First-line treatment	Topical glucocorticoids ● High-potent: clobetasol propionate, once daily, up to one month *or* ● Medium-potent: mometasone furoate, once daily, up to three months *Alternatively:* ● Calcipotriol, topically, 1-2 times a day (maybe combined with glucocorticoids) *or* ● Calcineurin inhibitor, topically, 1-2 times a day
Second-line treatment (instead of/additional to the first-line)	● P.U.V.A. therapy: either oral, bath or creme, 2-4 times a week, minimum of 30 U.V. irradiations ● UVA1 therapy: 50-80J/cm^2, 3-5 times a week, minimum of 30 U.V. irradiations

Table 3. Treatment of L.S. subtypes with severe skin and/or musculoskeletal involvement [8,74]

Adults	
First-line treatment	● Methotrexate, 12.5-25 mg/week
Second-line treatment (instead of/additional to the first-line)	● Methylprednisolone, *i.v.*, 500-1000 mg/day, on three consecutive days per month, up to 3-6 months *or* ● Prednisolone, *p.o.*, 0.5-2 mg/kg body weight/day, for 2-4 weeks, followed by the dosage tapering
Children	
First-line treatment	● Methotrexate, 15 mg/m^2 body surface area/week, max. 25 mg/week
Second-line treatment (instead of/additional to the first-line)	● Methylprednisolone, *i.v.*, 30 mg/kg body weight/day, max. 60 mg/day, on three consecutive days per month, for at least 3-6 months *or* ● Prednisolone, *p.o.*, 0.5-2 mg/kg body weight/day, max. 60 mg/day, for 2-4 weeks, followed by the dosage tapering

Systemic treatment is recommended in patients with severe skin lesions and deeper structures, including fat tissue, fascia, muscles, joints, or bones (table 3).

The therapy should last at least 12 months. The efficacy of systemic glucocorticoids treatment may be evaluated not sooner than 8-12 weeks from the course start since this is an average time for the skin sclerosis to begin a reduction. In severe patients, surgical intervention may be necessary, however, guidelines focus on the pharmacological agents as a base for the L.S. treatment [74].

Conclusions

Localized scleroderma only in the last decade has received proper interest among scientists and physicians. The development of standardized diagnostic and management guidelines brought tools for practitioners, aiding in the difficult task of recognizing the disease. Present-day strategies involving topical-, systemic- and phototherapy were confirmed by research as effective in morphea. The regimen must be suitable for specific patients, regarding age, disease form and severity, and whether changes are limited only to skin or advancing to deeper tissues. Recent discoveries in molecular pathways in rheumatic diseases create opportunities to develop targeted biological therapies that may halt disease progress from an early stage. At the same time, ongoing trials with already existing drugs can give doctors new means to handle affected that are not responding to currently available drugs. Further studies should also focus on patients' overall quality of life improvement.

References

1. Rodríguez-Salgado P., García-Romero M.T.: Morphea: a practical review of its diagnosis, classification and treatment. Gaceta medica de Mexico, 2019, 155(5), 483–491.
2. Florez-Pollack S., Kunzler E., Jacobe H.T.: Morphea: Current concepts. Clinics in dermatology, 2018, 36(4), 475–486.
3. Peroni A., Zini A., Braga V., Colato C., Adami S., Girolomoni G.: Drug-induced morphea: report of a case induced by balicatib and review of the literature. Journal of the American Academy of Dermatology, 2008, 59(1), 125–129.
4. Careta M.F., Romiti R.: Localized scleroderma: clinical spectrum and therapeutic update. Anais brasileiros de dermatologia, 2015, 90(1), 62–73.

5. Fett N., Werth V.P.: Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. Journal of the American Academy of Dermatology, 2011, 64(2), 217–230.
6. Laxer R.M., Zulian F.: Localized scleroderma. Current opinion in rheumatology, 2006, 18(6), 606–613.
7. Kreuter A., Krieg T., Worm M., Wenzel J., Moinzadeh P., Kuhn A., Aberer E., Scharffetter-Kochanek K., Horneff G., Reil E., Weberschock T., Hunzelmann N.: German guidelines for the diagnosis and therapy of localized scleroderma. Journal der Deutschen Dermatologischen Gesellschaft (Journal of the German Society of Dermatology), 2016, 14(2), 199–216.
8. Knobler R., Moinzadeh P., Hunzelmann N., Kreuter A., Cozzio A., Mouthon L., Cutolo M., Rongioletti F., Denton C.P., Rudnicka L., Frasin L.A., Smith V., Gabrielli A., Aberer E., Bagot M., Bali G., Bouaziz J., Braae Olesen A., Foeldvari I., Frances C., Jalili A., Just U., Kähäri V., Kárpáti S., Kofoed K., Krasowska D., Olszewska M., Orteu C., Panelius J., Parodi A., Petit A., Quaglino P., Ranki A., Sanchez Schmidt J.M., Seneschal J., Skrok A., Sticherling M., Sunderkötter C., Taieb A., Tanew A., Wolf P., Worm M., Wutte N.J., Krieg T.: European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: localized scleroderma, systemic sclerosis and overlap syndromes. Journal of the European Academy of Dermatology and Venereology, 2017, 31(9), 1401–1424.
9. Marzano A.V., Menni S., Parodi A., Borghi A., Fuligni A., Fabbri P., Caputo R.: Localized scleroderma in adults and children. Clinical and laboratory investigations on 239 cases. European journal of dermatology, 2003, 13(2), 171–176.
10. Horger M., Fierlbeck G., Kuemmerle-Deschner J., Tzaribachev N., Wehrmann M., Claussen C.D., Fritz J.: MRI findings in deep and generalized morphea (localized scleroderma). American journal of roentgenology, 2008, 190(1), 32–39.
11. Kroft E.B., Groeneveld T.J., Seyger M.M., de Jong E.M.: Efficacy of topical tacrolimus 0.1% in active plaque morphea: randomized, double-blind, emollient-controlled pilot study. American journal of clinical dermatology, 2009, 10(3), 181–187.
12. Stefanaki C., Stefanaki K., Kontochristopoulos G., Antoniou C., Stratigos A., Nicolaidou E., Gregoriou S., Katsambas A.: Topical tacrolimus 0.1% ointment in the treatment of localized scleroderma. An open label clinical and histological study. The Journal of dermatology, 2008, 35(11), 712–718.

13. Mancuso G., Berdondini R.M.: Localized scleroderma: response to occlusive treatment with tacrolimus ointment. The British journal of dermatology, 2005, 152(1), 180–182.
14. Zwischenberger B.A., Jacobe H.T.: A systematic review of morphea treatments and therapeutic algorithm. Journal of the American Academy of Dermatology, 2011, 65(5), 925–941.
15. Cantisani C., Miraglia E., Richetta A.G., Mattozzi C., Calvieri S.: Generalized morphea successfully treated with tacrolimus 0.1% ointment. Journal of drugs in dermatology, 2013, 12(1), 14–15.
16. Dytoc M.T., Kossintseva I., Ting P.T.: First case series on the use of calcipotriol-betamethasone dipropionate for morphoea. The British journal of dermatology, 2007, 157(3), 615–618.
17. Pope E., Laxer R.M.: Diagnosis and management of morphea and lichen sclerosus and atrophicus in children. Pediatric clinics of North America, 2014, 61(2), 309–319.
18. Stănescu L., Vâlcea A., Popescu C.F., Niculescu C.E., Ciobanu O., Călin G.: Plaque-type morphea in children. Romanian journal of morphology and embryology, 2010, 51(3), 559–563.
19. Cunningham B.B., Landells I.D., Langman C., Sailer D.E., Paller A.S.: Topical calcipotriene for morphea/linear scleroderma. Journal of the American Academy of Dermatology, 1998, 39(2 Pt 1), 211–215.
20. Santos G., Sousa L., João A., Paiva Lopes M.J.: Linear morphea - A case treated with calcipotriol and betamethasone dipropionate. European Journal Of Pediatric Dermatology, 2012, 22(4), 284.
21. Ascari-Raccagni A., Dondas A., Dubini A., Righini M.G., Trevisan G.: Biopsy proven morphea treated with tacalcitol ointment: case report. Acta dermatovenerologica Croatica, 2010, 18(4), 248–251.
22. Mertens J.S., Seyger M.M.B., Thurlings R.M., Radstake T.R.D.J., de Jong E.M.G.J.: Morphea and Eosinophilic Fasciitis: An Update. American journal of clinical dermatology, 2017, 18(4), 491–512.
23. Kreuter A., Gambichler T., Avermaete A., Jansen T., Hoffmann M., Hoffmann K., Altmeyer P., von Kobyletzki G., Bacharach-Buhles M.: Combined treatment with calcipotriol ointment and low-dose ultraviolet A1 phototherapy in childhood morphea. Pediatric dermatology, 2001, 18(3), 241–245.

24. Gambichler T., Kreuter A., Rotterdam S., Altmeyer P., Hoffmann K.: Linear scleroderma 'en coup de sabre' treated with topical calcipotriol and cream psoralen plus ultraviolet A. Journal of the European Academy of Dermatology and Venereology, 2003, 17(5), 601–602.
25. Campione E., Paternò E.J., Diluvio L., Orlandi A., Bianchi L., Chimenti S.: Localized morphea treated with imiquimod 5% and dermoscopic assessment of effectiveness. The Journal of dermatological treatment, 2009, 20(1), 10–13.
26. Dytoc M., Ting P.T., Man J., Sawyer D., Fiorillo L.: First case series on the use of imiquimod for morphoea. The British journal of dermatology, 2005, 153(4), 815–820.
27. Dytoc M., Wat H., Cheung-Lee M., Sawyer D., Ackerman T., Fiorillo L.: Evaluation of the efficacy and safety of topical imiquimod 5% for plaque-type morphea: a multicenter, prospective, vehicle-controlled trial. Journal of cutaneous medicine and surgery, 2013, 19(2), 132–139.
28. Joly P., Bamberger N., Crickx B., Belaich S.: Treatment of severe forms of localized scleroderma with oral corticosteroids: follow-up study on 17 patients. Archives of dermatology, 1994, 130(5), 663–664.
29. Amy de la Bretèque M., Rybojad M., Cordoliani F., Petit A., Juillard C., Flageul B., Bagot M., Bouaziz J.D.: Relapse of severe forms of adult morphea after oral corticosteroid treatment. Journal of the European Academy of Dermatology and Venereology, 2013, 27(9), 1190–1191.
30. Valančienė G., Jasaitienė D., Valiukevičienė S.: Pathogenesis and treatment modalities of localized scleroderma. Medicina (Kaunas, Lithuania), 2010, 46(10), 649–656.
31. Kroft E.B., de Jong E.M., Evers A.W.: Psychological distress in patients with morphea and eosinophilic fasciitis. Archives of dermatology, 2009, 145(9), 1017–1022.
32. Hawk A., English J.C.: 3rd. Localized and systemic scleroderma. Seminars in cutaneous medicine and surgery, 2001, 20(1), 27–37.
33. Zulian F., Martini G., Vallongo C., Vittadello F., Falcini F., Patrizi A., Alessio M., La Torre F., Podda R.A., Gerloni V., Cutrone M., Belloni-Fortina A., Paradisi M., Martino S., Perilongo G.: Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. Arthritis and rheumatism, 2011, 63(7), 1998–2006.
34. Koch S.B., Cerci F.B., Jorizzo J.L., Krowchuk D.P.: Linear morphea: a case series with long-term follow-up of young, methotrexate-treated patients. The Journal of

dermatological treatment, 2013, 24(6), 435–438.

35. Uziel Y., Feldman B.M., Krafchik B.R., Yeung R.S., Laxer R.M.: Methotrexate and corticosteroid therapy for pediatric localized scleroderma. The Journal of pediatrics, 2000, 136(1), 91–95.
36. Kreuter A., Gambichler T., Breuckmann F., Rotterdam S., Freitag M., Stuecker M., Hoffmann K., Altmeyer P.: Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. Archives of dermatology, 2005, 141(7), 847–852.
37. Seyger M.M., van den Hoogen F.H., de Boo T., de Jong E.M.: Low-dose methotrexate in the treatment of widespread morphea. Journal of the American Academy of Dermatology, 1998, 39(2 Pt 1), 220–225.
38. Torok K.S., Arkachaisri T.: Methotrexate and corticosteroids in the treatment of localized scleroderma: a standardized prospective longitudinal single-center study. The Journal of rheumatology, 2012, 39(2), 286–294.
39. Mertens J.S., van den Reek J.M., Kievit W., van de Kerkhof P.C., Thurlings R.M., Radstake T.R., Seyger M.M., de Jong E.M.: Drug Survival and Predictors of Drug Survival for Methotrexate Treatment in a Retrospective Cohort of Adult Patients with Localized Scleroderma. Acta dermato-venereologica, 2016, 96(7), 943–947.
40. Martini G., Ramanan A.V., Falcini F., Girschick H., Goldsmith D.P., Zulian F.: Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. Rheumatology (Oxford, England), 2009, 48(11), 1410–1413.
41. Mertens J.S., Marsman D., van de Kerkhof P.C., Hoppenreijs E.P., Knaapen H.K., Radstake T.R., de Jong E.M., Seyger M.M.: Use of Mycophenolate Mofetil in Patients with Severe Localized Scleroderma Resistant or Intolerant to Methotrexate. Acta dermato-venereologica, 2016, 96(4), 510–513.
42. Hassani J., Feldman S.R.: Phototherapy in Scleroderma. Dermatology and therapy, 2016, 6(4), 519–553.
43. Chaowattanapanit S., Choonhakarn C., Foocharoen C., Julanon N.: Phototherapy in systemic sclerosis: Review. Photodermatology, photoimmunology & photomedicine, 2017, 33(6), 296–305.
44. Shenoi S.D., Prabhu S., Indian Association of Dermatologists, Venereologists and Leprologists: Photochemotherapy (P.U.V.A.) in psoriasis and vitiligo. Indian journal of

dermatology, venereology and leprology, 2014, 80(6), 497–504.

45. Aboul-Enein H.Y., Kladna A., Kruk I., Lichszteld K., Michalska T.: Effect of psoralens on Fenton-like reaction generating reactive oxygen species. Biopolymers, 2003, 72(1), 59–68.
46. Aberer E, Kollegger H, Kristoferitsch W, Stanek G. Neuroborreliosis in morphea and lichen sclerosus et atrophicus. Journal of the American Academy of Dermatology, 1988, 19(5 Pt 1), 820–825.
47. Brinckmann J., Neess C.M., Gaber Y., Sobhi H., Notbohm H., Hunzelmann N., Fietzek P.P., Müller P.K., Risteli J., Gebker R., Scharffetter-Kochanek K.: Different pattern of collagen cross-links in two sclerotic skin diseases: lipodermatosclerosis and circumscribed scleroderma. The Journal of investigative dermatology, 2001, 117(2), 269–273.
48. Pavlotsky F., Sakka N., Lozinski A., Barzilai A.: Bath psoralen-UVA photochemotherapy for localized scleroderma: experience from a single institute. Photodermatology, photoimmunology & photomedicine, 2013, 29(5), 247–252.
49. Grundmann-Kollmann M., Ochsendorf F., Zollner T.M., Spieth K., Sachsenberg-Studer E., Kaufmann R., Podda M.: PUVA-cream photochemotherapy for the treatment of localized scleroderma. Journal of the American Academy of Dermatology, 2000, 43(4), 675–678.
50. Krenitsky A., Ghamrawi R. I., Feldman S. R.: Phototherapy: a Review and Update of Treatment Options in Dermatology. Current Dermatology Reports, 2020, 9, 10–21.
51. El-Mofty M., Zaher H., Bosseila M., Yousef R., Saad B.: Low-dose broadband UVA in morphea using a new method for evaluation. Photodermatology, photoimmunology & photomedicine, 2000, 16(2), 43–49.
52. Sawada H., Isogai Z., Morita A.: Altered decorin expression of systemic sclerosis by UVA1 (340-400 nm) phototherapy: immunohistochemical analysis of 3 cases. B.M.C. dermatology, 2003, 3, 2.
53. Gambichler T., Skrygan M., Tomi N.S., Breuksch S., Altmeyer P., Kreuter A.: Significant downregulation of transforming growth factor-beta signal transducers in human skin following ultraviolet-A1 irradiation. The British journal of dermatology, 2007, 156(5), 951–956.
54. De Rie M.A., Bos J.D.: Photochemotherapy for systemic and localized scleroderma. Journal of the American Academy of Dermatology, 2000, 43(4), 725–726.

55. Vielhaber G., Grether-Beck S., Koch O., Johncock W., Krutmann J.: Sunscreens with an absorption maximum of > or =360 nm provide optimal protection against UVA1-induced expression of matrix metalloproteinase-1, interleukin-1, and interleukin-6 in human dermal fibroblasts. Photochemical & photobiological sciences: Official journal of the European Photochemistry Association and the European Society for Photobiology, 2006, 5(3), 275–282.
56. Takeda K., Hatamochi A., Arakawa M., Ueki H.: Effects of tumor necrosis factor-alpha on connective tissue metabolism in normal and scleroderma fibroblast cultures. Archives of dermatological research, 1993, 284(8), 440–444.
57. Nisar M.F., Parsons K.S., Bian C.X., Zhong J.L.: UVA irradiation induced heme oxygenase-1: a novel phototherapy for morphea. Photochemistry and photobiology, 2015, 91(1), 210–220.
58. Vasquez R., Jabbar A., Khan F., Buethe D., Ahn C., Jacobe H.: Recurrence of morphea after successful ultraviolet A1 phototherapy: A cohort study. Journal of the American Academy of Dermatology, 2014, 70(3), 481–488.
59. Kreuter A., Hyun J., Stücker M., Sommer A., Altmeyer P., Gambichler T.: A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. Journal of the American Academy of Dermatology, 2006, 54(3), 440–447.
60. Kumar A.B., Blixt E.K., Drage L.A., El-Azhary R.A., Wetter D.A.: Treatment of morphea with hydroxychloroquine: A retrospective review of 84 patients at Mayo Clinic, 1996-2013. Journal of the American Academy of Dermatology, 2019, 80(6), 1658–1663.
61. Bali G., Frühauf J., Wutte N., Aberer E.: Cyclosporine Reduces Sclerosis in Morphea: A Retrospective Study in 12 Patients and a Literature Review. Dermatology (Basel, Switzerland), 2016, 232(4), 503–510.
62. Zulian F., Culpo R., Sperotto F., Anton J., Avcin T., Baildam E.M., Boros C., Chaitow J., Constantin T., Kasapcopur O., Knupp Feitosa de Oliveira S., Pilkington C.A., Russo R., Toplak N., van Royen A., Saad Magalhães C., Vastert S.J., Wulffraat N.M., Foeldvari I.: Consensus-based recommendations for the management of juvenile localised scleroderma. Annals of the rheumatic diseases, 2019, 78(8), 1019–1024.
63. Lythgoe H., Baildam E., Beresford M.W., Cleary G., McCann L.J., Pain C.E.: Tocilizumab as a potential therapeutic option for children with severe, refractory

juvenile localized scleroderma. Rheumatology (Oxford, England), 2018, 57(2), 398–401.

64. Massachusetts General Hospital, Regeneron Pharmaceuticals: Study to Assess Sarilumab in Halting Progression of Morphea. https://clinicaltrials.gov/ct2/show/NCT03679845?term=monoclonal&cond=Morphea&draw=2&rank=1 (data pobrania 29.07.2021).
65. Stausbøl-Grøn B., Olesen A.B., Deleuran B., Deleuran M.S.: Abatacept is a promising treatment for patients with disseminated morphea profunda: presentation of two cases. Acta dermato-venereologica, 2011, 91(6), 686–688.
66. Hirohata A., Hanafusa T., Igawa K., Inoue-Nishimoto T., Mabuchi-Kiyohara E., Nishide M., Yokozeki H., Ikegami R.: Oral tacrolimus for the treatment of generalized morphea. European journal of dermatology, 2016, 26(1), 112–113.
67. Frumholtz L, Roux J, Bagot M, Rybojad M, Bouaziz JD. Treatment of Generalized Deep Morphea With Everolimus. J.A.M.A. dermatology, 2016, 152(10), 1170–1172.
68. Coelho-Macias V., Mendes-Bastos P., Assis-Pacheco F., Cardoso J.: Imatinib: a novel treatment approach for generalized morphea. International journal of dermatology, 2014, 53(10), 1299–1302.
69. Inamo Y., Ochiai T.: Successful combination treatment of a patient with progressive juvenile localized scleroderma (morphea) using imatinib, corticosteroids, and methotrexate. Pediatric dermatology, 2013, 30(6), e191–e193.
70. Diab M., Coloe J.R., Magro C., Bechtel M.A.: Treatment of recalcitrant generalized morphea with infliximab. Archives of dermatology, 2010, 146(6), 601–604.
71. Chimenti M.S., Teoli M., Di Stefani A., Giunta A., Esposito M., Perricone R.: Resolution with rituximab of localized scleroderma occurring during etanercept treatment in a patient with rheumatoid arthritis. European journal of dermatology, 2013, 23(2), 273–274.
72. Constantin T., Foeldvari I., Pain C.E., Pálinkás A., Höger P., Moll M., Nemkova D., Weibel L., Laczkovszki M., Clements P., Torok K.S.: Development of minimum standards of care for juvenile localized scleroderma. European journal of pediatrics, 2018, 177(7), 961–977.
73. Schoch J.J., Schoch B.S., Werthel J.D., McIntosh A.L., Davis D.M.R.: Orthopedic complications of linear morphea: Implications for early interdisciplinary care. Pediatric dermatology, 2018, 35(1), 43–46.

74. Białynicki-Birula R., Reszke R.: Autoimmunologiczne choroby tkanki łącznej. Twardzina ograniczona. [w:] Terapia w dermatologii. Szepietowski J., Baran W. (red.). PZWL Wydawnictwo Lekarskie, Warszawa, 2019, 248-253.

A novel immunotherapy — Car T-Cell therapy as a chance for revolutionizing in oncology

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Abbreviation list

- 137aAPC - artificial antigen-presenting cell
- 4-1BB - Cluster of Differentiation
- ALL - acute lymphoblastic leukemia
- ALL-B - B- Cell Acute Lymphoblastic Leukemia
- APC - antigen-presenting cell
- ATMP - advanced therapy medicinal product
- BCMA - B-cell maturation antigen
- BTK - Bruton's tyrosine kinase
- CAR - chimeric antigen receptor
- CAR-IS - chimeric antigen receptor immune synapse
- CAR-T - chimeric antigen receptor T cell
- CD - Cluster of Differentiation
- CLL - chronic lymphocytic leukemia
- CRP - C-reactive protein
- CRS - cytokine release syndrome
- DLBCL - diffuse large B cell lymphoma
- DLI - donor-lymphocyte infusion
- DNA - deoxyribonucleic acid
- EMA - European Medicines Agency
- ESMO - European Society for Medical Oncology
- E.U. – European Union

- FDA - The United States Food and Drug Administration
- FL - follicular lymphoma
- GD2 - disialoganglioside-2
- GVHD - graft-versus-host disease
- HER2 - human epidermal growth factor receptor- 2
- HGBL - high grade B-cell lymphoma
- HIV - human immunodeficiency virus
- HLA - human leukocyte antigens
- HLH - hemophagocytic lymphohistiocystosis
- ICANS - immune effector cell-associated neurotoxicity syndrome
- IFN- ɣ -interferon-gamma
- I.L.- interleukin
- I.S. - immune synapse
- LDH - lactate dehydrogenase
- MAS - macrophage activation syndrome
- MCL - mantle cell lymphoma
- MM - multiple myeloma
- PFS - progression-free survival
- PMBCL - primary mediastinal B-cell lymphoma
- RNA - Ribonucleic acid
- ScFv - single-chain variable fragment
- sIL- 2 - soluble interleukin-2
- TAA - tumor associated antigen
- TCR - T-cell receptor
- USA – The United States of America

Therapeutic approach to the treatment of cancer

Cancer treatment is currently one of the greatest challenges in modern medicine. The revolution in the therapeutic approach began in the 1960s and continues to this day. The beginning of pharmacological treatment dates back to the 20th century [1,2]. Most of the currently used chemotherapeutic agents rely on non-selective blockers of mitosis, intensively

dividing cells in the human body. Due to this fact, both cancer cells and healthy cells are destroyed. Therefore, cancer treatment is associated with a high percentage of side effects. The treatment regimens used include surgical removal, chemotherapy, radiation therapy, immunotherapy, and targeted therapy. For several decades, a specific treatment strategy has been defined for each type and stage of cancer, allowing the patient to function in the best possible way [3]. The aforementioned immunomodulating treatment and targeted therapies are breakthrough solutions in a new branch of medicine, i.e., immuno-oncology. The main goal of immuno-oncology is to support the human immune system in the fight against cancer. Unlike traditional chemotherapy, cancer immunotherapy does not directly destroy cancer cells through a toxic effect but activates the body's immunity and natural defenses. Immunotherapy is a set of methods based on modifying the functioning of the immune system. It uses mechanisms such as immunosuppression, immune reconstruction, or immunostimulation. Immunotherapy is a relatively new therapeutic approach. Nevertheless, some diseases have developed an effective treatment regimen based exclusively on immunotherapy. For example, monotherapy based on immunomodulation is extremely effective, including hematological cancers, i.e., chronic lymphocytic leukemia, non-Hodgkin's lymphoma or myelodysplastic syndrome [4].

How CAR T-cell therapy works

Combining the immunotherapy mentioned above with targeted therapy is the greater achievement that should be associated with the future of modern immuno-oncology. This method is used in a therapy based on chimeric antigen receptors T cells (CAR-T). The essence of CAR-T therapy is to use the antitumor properties of T cells by equipping them with chimeric antigen receptors (CAR). CAR-T was first developed in 2015. Three years later, in 2018, it was approved by the European Medicines Agency (EMA) in the central registration procedure for the advanced therapy medicinal product (ATMP) Kymriah (tisagenlecleucel). The basis for registration was the results of the ELIANA and JULIET studies published in the New England Journal of Medicine [5,6].

Immune receptors and foreign antigens

The main function of the T cells is to destroy any "unwanted" cells in the human body, i.e., foreign cells infected by virus or neoplastic cells. The T cells recognize them by finding

proteins called antigens on their surface and linking them with appropriate receptors. Activated in such a way, T cells trigger other parts of the immune system to destroy the foreign substance. Nowadays, thanks to biomedical engineering, it has become possible to modify the patient's lymphocytes in such a way as to increase their affinity for cancer. The artificial modification of T cells makes it possible to target them against specific molecules on cancer cells. The receptor added by genetic modification is called chimeric antigen receptors (CAR). It allows triggering a cytotoxic reaction to a specific cell in the human body.

T cell cytotoxicity

The death of the cell that has been recognized by T cells occurs as a consequence of the T cells' cytotoxicity. After an antigen is recognized by the T-cell, combining T-cell receptor (TCR) with an antigen initiates the generation of the classical immune synapse (I.S.). During CAR-T therapy, CAR acts as a TCR and forms CAR immune synapse (CAR-IS). The formation of the I.S. starts the signaling pathway consists of actin accumulation and polarization of the microtubule-organizing center [7,8]. Consequently, the cytolytic granules with perforins and granzymes attached to the microtubules migrate towards the T lymphocyte surface and fuse with plasma membrane within the central area of the synapse. Substances from the granules are released into the synaptic cleft. Perforins create channels in the cell membrane of the target cell, through which granzymes that activate caspase-dependent and independent apoptotic cell death enter the cytoplasm [8]. The targeted action makes CAR-T the most advanced cellular therapy, offering hope for patients and physicians to treat chemoresistant and relapsed forms of the disease.

Indications for the use of CAR-T therapy

The CD19-directed CAR-T therapy turned out to be effective in treating relapsed and refractory ALL. Complete remission was attained in 90% among such patients, with an estimated six-month EFS of 67% and overall survival of 78%. Thus, CAR-T is associated with a high remission rate, even among patients for whom stem-cell transplantation had failed, which is the most effective way of treatment for now. Moreover, durable remissions up to 24 months were observed [9]. Other studies confirm that CAR-T is highly effective and achieve 80-90% of complete remission among patients with refractory or resistance ALL-B [10].

Considering all mentioned researches, we can assume that this type of treatment can be

very helpful in treating some types of cancer, even when other treatments are no longer working.

Making the CAR T cells

Collecting the T cells

T cell therapy starts with obtaining the patient's leukocytes by leukapheresis, an apheresis method that separates leukocytes from whole blood. Currently, active clinical trials and trials that led to approved commercial products required an absolute lymphocyte count of 100 – 200 / ml. The blood components are usually separated by density with continuous or intermittent centrifugation methods using density gradient media. Red blood cells and platelets are contaminations that are usually removed in a washing step. After washing, the cells are cryopreserved or delivered fresh to a manufacturing facility for processing. Processing includes T-cell expansion, genetic manipulation, quality control testing, and cryopreservation of the final expanded T-cell product [11,12,13].

After separation from the leukapheresis product, T cells are activated, transduced, and expanded *ex vivo*. The expansion process is mainly based on the use of growth factors, such as IL-2, beads coated with anti-CD3/anti-CD28 monoclonal antibodies, or cell-based artificial APCs (aAPCs). In the presence of interleukin-2 and aAPCs, T cells can grow logarithmically. Then, the beads, or aAPCs, can be easily removed from the culture through magnetic separation.

Genetic manipulation of patients' T cells is the transfection of them with a gene that encodes a CAR against the neoplasm cells. The CAR encoding gene is transduced into T cells, usually by using retroviral or lentiviral vectors. The vector introduces genetic material in the form of RNA. The RNA is reverse-transcribed into DNA and permanently integrates into the genome of the patient cells. Integration of transgene into the genome of T cells provides a stable and lasting expression of the receptor [14,15,16]. The process of T-cell processing can take 2–4 weeks [11,12,13].

Structure of the Chimeric antigen receptors (CARs)

Chimeric antigen receptor comprises four major domains, i.e., an extracellular antigen-recognition domain, a spacer domain, a transmembrane domain, and a cytoplasmic domain.

- The antigen-recognition domain is most frequently a single-chain variable fragment (scFv) derived from a monoclonal antibody. ScFv consists of the antibody variable light-

chain and variable heavy-chain connected by a peptide linker [17].

- The spacer domain is usually derived from the Fc fragment of an IgG antibody. However, Non-IgG–based spacers such as CD8 and CD28 hinge regions are also used. The spacer domain mediates the antigen-antibody reaction and affects the efficacy of binding to the antigen by giving scFv flexibility. Additionally, the length of the spacer domain determines the immune synapse distance, which influences the signaling [18].
- The transmembrane domain is derived from a transmembrane receptor protein, most commonly CD8 or CD28. Its role is to transmit the signal between the extracellular and intracellular domains and to anchor the receptor in the cell membrane [15,19].
- The number of cytoplasmic domains depends on CAR generation. First-generation CARs contained only an activating domain - typically the CD3-ζ chain of the T cell receptor-CD3 (TCR-CD3) complex. However, early CAR-T cell exhaustion could not achieve a satisfactory antitumor effect [17].

Under physiological conditions, the CD3-TCR complex, upon recognizing an antigen, produces a signal that initiates the signaling cascade leading to T cell activation. However, for optimal immune response, a second signal is required. It comes from costimulatory receptors and increases proliferation, cytotoxicity, memory formation, and prevents anergy. That is why the second and third-generation CARs contain one or two costimulatory domains, respectively, which are most often derived from CD28 and 4-1BB whether the third generation provides greater clinical benefits than the second-generation CARs [20].

Choice of the target

Identifying the appropriate antigen to be targeted by CAR-T cells is essential in designing an effective therapy. An ideal target antigen should provide both efficiency and safety, having wide coverage on tumour cells, and be highly specific to avoid damage to healthy cells ("on-target, off-tissue" effect). CD19 is the antigen most commonly used in CAR-T therapies today. It is a typical antigen of B cells surface. Therefore, the antigen
has excellent coverage for B cell malignancies but is not specific to all neoplastic cells [21]. In this case, CAR-T therapy is associated with long-term B cells aplasia. Even so, it can be well managed by using intravenous immunoglobulin [22]. However, it needs to be added that stability of the target expression is also an important factor in selecting the good one. Loss of antigen expression (target loss) is a common reason for the failure of CAR-T therapy [21].

Receiving the CAR T-cell infusion

Preparation of the patient

The efficacy of CAR-T therapy largely depends on CAR-T cells expansion and persistence in the patient. All patients undergoes lymphodepleting chemotherapy before infusion of CAR-T cells. Lymphodepletion reduces tumour volume, eradicates endogenous regulatory T-cells to amplify CAR-T cell responses, eliminates other immune cells that may compete for homeostatic cytokines, and enhances the activation of APCs [23,24]. Cytophysiological effects of lymphodepletion contribute to increase the availability of homeostatic cytokines, i.e., interleukin-7 (IL-7) and interleukin-15 (IL-15), that promote transferred T cells survival and increases their expansion [25]. Incomplete lymphodepletion may result in limited persistence of CAR-T cells. Meta-analysis showed that patients who received a lymphodepletion regimen before cell infusion achieved a 6-month progression-free survival (PFS) rate of 94.6%. In contrast, patients who did not received lymphodepletion regimen only achieved a PFS rate of 54.5% ($p < 0.001$) [26]. Currently, the most commonly used regimen is the F.C. regimen, including fludarabine and cyclophosphamide.

After administration lymphodepletion regimen, modified T-cells are infused back into the patient as therapy. The number of CAR-T cells injected also is important. The 6-month PFS for patients infused more than 10^8 CAR-T cell was 94.4%, significantly higher than 58.6% in patients infused less than 10^8 CAR-T cell ($P < 0.001$) [26]. Following infusion, CAR-T cells are activated by the tumour antigen recognition. Then, they vastly proliferate and start to exert cytotoxicity against tumour cells. CAR-T cells reach their peak blood concentration usually within 7 to 14 days. The concentration declines over the next few months. However, CAR-T cells show long-term persistence in some patients after dropping and are detectable even years after infusion [25].

Monitoring after CAR T-cell infusion

Following infusion, patients are monitored for toxicities associated with CAR-T cells. There are two major critical points during the CAR-T cells therapy when it is vital to recognise and adjust or even stop their activity. The first moment is soon after the CAR-T cells transfer in case of severe, untreatable side effects, i.e., anaphylaxis. The second is a late one when CAR-T cells have eliminated the tumour cells and continue to attack cross-reactive healthy tissue

[27]. The main adverse events include cytokine release syndrome (CRS), macrophage activation syndrome (MAS), hemophagocytic lymphohistiocytosis, (HLH), or neurotoxicity. Because of the risk of these side effects, adult patients are typically advised not to drive, operate heavy machinery, or do any other potentially dangerous activities for at least several weeks after getting treatment.

Possible CAR T-cell therapy side effects

Cytokine release syndrome (CRS)

Cytokine-release syndrome is the most common adverse effect of CAR T-cell therapy. Following infusion, activation of transferred CAR-T cells leads to the production of supraphysiologic levels of the cytokine. CRS typically occurs within the first week after CAR T-cell therapy and generally peaks within one to two weeks of cell administration. During the first week, the levels of interferon-gamma (IFN- ɣ), interleukin-6 (IL-6), soluble interleukin-2 (sIL-2), interleukin-8 (IL-8) and interleukin-10 (IL-10) raise. This cytokine storm elevation triggers cytokine release syndrome, which is a temporary and reversible systemic inflammatory state. Patients with CRS suffer from hypotension, high fever, malaise, headaches, myalgias, arthralgias, anorexia, nausea, neurological disturbances, respiratory distress, hypoxia, and capillary leak syndrome [11]. The high levels of C-reactive protein (CRP), IL-6, and IFN- ɣ have been stated as predictive serum biomarkers for CRS [28,29]. Moreover, the high levels of IL-6 have strongly correlated with the severity of CRS [27]. The management of CRS has as its basis the grade, which includes components of temperature, systolic blood pressure, oxygen saturation, and possible toxicity to other organs. The primary points for management include corticosteroids and IL-6 antagonists and supportive care, i.e., acetaminophen and hypothermia blanket for fever, intravenous fluid for dehydration or hypotension, supplemental oxygen [30].

Macrophage Activation Syndrome (MAS) and Hemophagocytic Lymphohistio-cystosis (HLH)

A subset of patients who suffer from CRS also manifest symptoms similar to MAS or HLH, which manifest as liver dysfunction with hepatosplenomegaly and coagulopathic with decreased fibrinogen levels. The appearance of these syndromes is triggered by immune dysregulation and leads to full-body toxicity. High serum cytokines such as IFNγ lead to

macrophage activation [31]. Identification of CRS-related MAS or HLH is complicated due to similar pathogenesis. Therefore, these syndromes are challenging to differentiate and diagnose in patients who receive CAR T-cells. However, MAS can be distinguished from CRS by the decrease in fibrinogen and the rapid rise of ferritin and LDH. This immunologic toxicity can be mitigated with steroids, anakinra, and supportive care, and patients ultimately have similar survival compared to patients without MAS-L. Although those are serious adverse events, the frequency of HLH/MAS in CAR-T-treated patients has been reported to be as low as ~1% [32].

Neurotoxicity

Neurotoxicity is developed in a substantial portion of patients treated with CD19-targeted T cells; due to its origin there was identified an immune effector cell-associated neurotoxicity syndrome (ICANS), symptoms of which are as follows: visual hallucinations, encephalopathy (confusion, delirium), dysphasia, word-finding aphasia, motor weakness, tremor, headaches, depressed level of consciousness, epilepsy or coma [11]. In addition, encephalopathy in children may be observed as increased irritability to delirium in adolescents [28]. Another complication associated with neurotoxicity is endothelial dysfunction. It may appear in vascular instability, capillary leak, blood-brain barrier disruption, and disseminated intravascular coagulation [33]. Even though neurotoxicity has been reported to be self-limited with no long-term neurological effects for most patients, some death cases were observed due to neurotoxicity caused by cerebral oedema.

Other adverse events

Other possible serious side effects of CAR T-cell therapy include allergic reactions during the infusion, abnormal levels of minerals in the blood, a weakened immune system with an increased risk of serious infections, and low blood cell counts.

Anaphylaxis, as allergic reactions, may appear due to the immunogenicity caused by murine antibody derived single-chain variable fragment (ScFV), the humanizing components of the CAR protein may reduce though the chance of this severe allergic reaction to appear [29].

The weakening of the immune system is due to the affinity of antigens for healthy body tissues. On-target off-tumor toxicity occurs when T cells lose the ability to distinguish normal cells from tumour cells. Despite the high specificity of the treatment, biomarkers can be expressed in normal tissues and organs, especially lymphatic tissues, resulting in tissue damage.

Quite commonly observed due to CD19 CAR-T cell therapy is a B-cell aplasia resulting in hypogammaglobulinemia lead to weakened immune system [28,29,33].

The risk of "on-target off-tumor toxicity" increase in solid tumour therapy. For example, HER antigen is may have been a target antigen in breast cancers. Although, it is expressed also by cardiac and pulmonary epithelial cells. Therefore, HER2 CAR T-cells applied for breast cancer can exhibit cardiopulmonary toxicity. Moreover, a report reported that CAR T-cell therapy for colorectal cancer led to the patient's death because of pulmonary toxicity [29,34].

Tumor lysis syndrome is another toxicity that appears due to sudden or massive tumour cell death and manifests in increased lactate dehydrogenase, uric acid, and potassium levels [29]. It mostly appears in patients treated with CD19-targeted CAR T cells, especially those with chronic lymphocytic leukaemia (CLL). Alongside the tumor, lysis syndrome raises the risk of acute renal injury in the setting of renal dysfunction due to CRS [28].

Advantages of therapy in hematological malignancies

The most notable advantage of CAR-T cell therapy over other cancer therapies is the abrupt time intervention and a single infusion of CAR-T cells. This for the oncological patient is a major change compared to classical treatment methods, especially considering that after the infusion, only 2-3 weeks of proper care and observation is sufficient for the patient who does not perform any side effects of the treatment [34]. Another supremacy of CAR-T cell therapy over the standard treatment approach is that CAR-T cells target specific markers of B-cell lineage (CD 19). Which is not expressed on other cell lines; thus in contrast with adaptive immune cells, CAR-T cells can eliminate only cancer cells containing the corresponding, highly specific tumor-associated antigen (TAA), which to some extent allows avoiding the unnecessary killing of healthy tissues [29]. Furthermore, CAR-T cells can recognize cell surface molecules without the help of human leukocyte antigens (HLA) expression. This also decides on the predominance of CAR-T cell treatment since tumours often avoid T cell immune surveillance by hiding HLA or other molecules involved in antigen processing and presentation. What is more, the CAR-T cells can recognize potential antigens in nearly all forms, such as carbohydrate, lipid, and protein antigens, which can be combined explicitly by proper antibodies [33]. The activity of CAR-T cells does not limit to a short time of hospitality of the

patient. Its efficacy may persist for decades as the cells can survive in the host body in the long term, with a constant ability to find and destroy cancer cells e.g., during relapse [34].

This long-term efficiency of the CAR-T cells and its single infusion process leads to an advantage that needs to be looked at on the broad spectrum. The CAR-T cell therapy is an expensive but one-time procedure. Comparing the costs of this treatment with the costs that have to be borne over few courses of patient's therapy, during which he remains for long weeks or even months in the hospital, taking not so cheap medications, the overall price is not much smaller than the CAR-T cell therapy. Moreover, thanks to the CAR-T treatment, transplantation can be avoided, the costs of which are significantly high [5].

Types of CAR-T therapy

Approval and indications

The institutions responsible for accepting and approving new medical products and therapies in the USA and European Union are the FDA (The United States Food and Drug Administration) and the EMA (European Medicines Agency). Currently, in the USA, 5 CAR-T therapies are approved (Kymirah, Yescarta, Tecartus, Breyanzi, Abecma) [35,36,37,38,39], whereas in the E.U. just 3 (Kymirah, Yescarta, Tecartus) [40,41,42]. For now, the FDA has approved CAR T-cell therapy for adult patients with certain types of blood cancers, including aggressive, relapsed, or refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBL), relapsed refractory or transformed follicular lymphoma (F.L.), and mantle cell lymphoma (MCL), relapsed or refractory multiple myeloma (MM). In addition, CAR T-cell therapy is approved for patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL-B) up to age 25. The general recommendations for all CAR-T therapies specify that patients should be evaluated for active graft-versus-host disease (GVHD), uncontrolled infections, or recent donor-lymphocyte infusion (DLI) with a threshold of at least 6 weeks between DLI and CAR-T infusion. In addition, patients with uncontrolled infections and active grade II-IV GVHD should be excluded from CAR-T therapy [43].

Kymirah CAR-T

The first approved chimeric antigen receptor T-cell therapy (CAR-T therapy) in 2017

was tisagenlecleucel under the trade name Kymirah [36,43]. Kymirah is indicated in patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse after the stem cell transplantation. Second indication targets patients with relapsed or refractory large B- cell lymphoma after two or more lines of systematic therapy, including most patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified [43,44,45,46,47].

Yescarta CAR-T

The second CAR-T therapy - axicabtagene ciloleucel (Yescarta) was approved [38]. Yescarta is used for the treatment of DLBCL with the same indications as for tisagenlecleucel [45,46] or follicular lymphoma (F.L.) after at least two prior lines of systematic therapy [47,48], whereas the EMA approved it in treating DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) for adult patients with relapsed or refractory disease [41,44,47,49]. According to the ESMO (European Society for Medical Oncology), treatment with CAR-T in follicular lymphoma can lead to long-term remission in relapsed F.L., but up to date, it is recommended only for transformed F.L. (which is a registered indication) due to CAR-T therapy. Right now, treating indolent lymphoma with CAR-T is limited to clinical trials for refractory or relapsing patients with poor prognostic features [50].

Tecartus CAR-T

The last therapy approved by the EMA and the FDA is brexucabtagene autoleucel (Tecartus). It is applied to patients with mantle cell lymphoma. The main indication for CAR-T therapy is relapsed disease after at least two other treatments, including Bruton's tyrosine kinase (BTK) inhibitor [39,40,51].

Breyanzi and Abecma CAR-T

Therapies that are approved by the FDA but not by the EMA are Breyanzi and Abecma. There are still considerations about their approval in the E.U.

Breyanzi is a lisocabtagene maraleucel therapy that is indicated for patients with refractory or relapsed large B-cell lymphoma after at least two lines of systemic therapy. Indications include DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B [35].

The newest CAR-T therapy is idecabtagene vicleucel (Abecma) which was approved on March 26, 2021. Up to date, it is the only therapy that targets the BCMA (B-cell maturation antigen) instead of CD19. The indication for Abecma are patients with relapsed or refractory multiple myeloma, who have received at least four prior lines of therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody [37].

The CAR-T therapy is available in mentioned above commercial CAR T-cell products or clinical trials. If not candidates for clinical trials, patients with indications for treatment with commercial products undergo evaluation by financial coordinators with submission to insurance companies and, in most centers, internal hospital financial clearance. This is undoubtedly a high internal cost for most hospitals and a challenge they face [11,12,13].

Current limitations, the requirements

Under formal requirements, CAR-T therapy can be carried out only in qualified hemato-oncology centers with appropriate infrastructure, organizational base, and experience in hematopoietic stem cell transplantation. These centers only collect biological material from the patient and prepare it for shipment to the manufacturer's laboratory. Nowadays, in Poland, we have three centers, one for pediatric patients with acute lymphoblastic leukemia (ALL) and two for adults patients with ALL and diffuse large B-cell lymphoma (DLBCL) [5].

These hospitals that participate in a CAR-T therapy program must access apheresis for mononuclear cell collections and cell processing facilities for temporary storage. CAR T cells also have the potential for severe toxicities, including CRS and neurologic toxicities that require specialized teams in inpatient and outpatient settings. These include nursing, coordinators, physicians with expertise in CAR T-cell–associated toxicities, intensivists, and neurologists. Safe administration of these therapies also requires appropriate education, competencies, standard operating procedures, processes, and administrative oversight [11]. Therefore, the hospitals that participate in the program need to be adjusted to do apheresis for mononuclear cell collections and cell processing facilities for temporary storage. The process can take from 2 up to 4 weeks and after infusion, the patient must stay hospitalised for a week or even more depending on his response to treatment. Therefore the main disadvantage which comes along with a CAR-T treatment is a financial matter. Several therapies already available on the market are expensive, for example, $475 000 for Yescarta and $373 000 for Kymriah. Furthermore,

when the hospitalization expenses and the costs of drugs are added, the total cost increases to almost $1 500 000 per patient, making the treatment high-priced [34].

Potential strategies and future perspectives

The CAR-T method was introduced very recently. This therapeutic option was discovered only six years ago and has been gradually popularizing since then. Currently, there are only five CAR-T therapies approved by the FDA, and only three of them are used in Europe. Currently, the CAR-T therapy is used only as second choice or supportive treatment after systemic therapy in diseases such as ALL-B, DLBCL, FL, MCL, MM, or PMBCL.

Besides all the indications mentioned above, many other clinical trials of CAR-T therapy are conducted in the treatment of other types of blood cancer and solid tumors. Up to date, there are 1253 registered CAR-T clinical trials [52]. China is the leading country with 489 active studies, followed by the USA and the E.U. with 470 and 164 clinical trials. Among all of them, the status of 560 is recruiting, and 241 studies are completed, which clearly shows us the dynamics of CAR-T therapy development. Most of the studies focus on categories shown as "Neoplasms by Histologic Type", "Immunoproliferative Disorders" and "Lymphoproliferative Disorders", but the diversity of diseases that are considered as a potential indication for CART is broad. It is not restricted only to neoplasms but also is broaden by viral infections (e.g. HIV) or the usefulness of CAR-T therapy for patients after strokes. New studies target the CD19 like currently approved therapies (Kymirah, Yescarta, Tecartus, and Breyanzi) or BCMA (Abecma) and other receptors or markers such as CD7, CD22, CEA, or GD2. Many clinical trials are trying to improve CAR-T therapy by connecting it with INF- α or applying dual CAR-T cell therapy, in which, except for CD19, they are targeting, e.g., CD22 [52].

Thanks to the dynamic progress of clinical trials may contribute to the popularization of this therapy. As clinical trials progress, this method may become more popular in clinical practice. Consequently, its demand will increase, and the production of devices for modifying lymphocytes will decrease. Therefore, in a dozen years, we can expect cheaper and more widely used CAR-T therapies.

The CAR-T is a revolutionary, highly specialized therapy in cancer treatment, which outclasses current standard treatments by efficiency and quality of patient life and gives great hope for future treatment methods. Without a doubt, CAR-T therapy has brought

haematological malignancies' treatment into a new era. The positive outcome of the clinical trials gives much promise.

References

1. Williams K.J.: The introduction of chemotherapy using arsphenamine the first magic bullet. Journal of the Royal Society of Medicine, 2009, 102(8), 343–348.
2. DeVita V.T., Chu E.: A history of cancer chemotherapy. Cancer Research, 2008, 68(21), 8643–8653.
3. Strąg-Lemanowicz A., Leppert W.: Rola onkologicznego leczenia systemowego u pacjentów z zaawansowaną chorobą nowotworową. Palliative Medicine in Practice, 2014, 8(1), 11–22.
4. Dmoszyńska A.: Leki immunomodulujące – przełom w leczeniu nowotworów hematologicznych. Acta Haematologica Polonica, 2013, 44(4), 370–377.
5. Czech M., Jakub G., Skrzekowska-Baran I., Bondaryk K.: Wartość i miejsce w systemie ochrony zdrowia terapii komórkowych i genowych na przykładzie CAR-T. Wydawnictwo Novartis, Warszawa, 2020.
6. Summary of the ELIANA and JULIET research results https://www.novartis.com/news/media-releases/novartis-announces-longer-term-analyses-from-pivotal-kymriah-trials-showed-durable-responses-are-maintained-patients-advanced-blood-cancers (cited: 13.07.2021).
7. Wu L., Wei Q., Brzostek J., Gascoigne N. R. J.: Signaling from T cell receptors (TCRs) and chimeric antigen receptors (CARs) on T cells. Cellular and Molecular Immunology, 2020, 17(6), 600–612.
8. Benmebarek M.-R., Karches C.H., Cadilha B.L., Lesch S., Endres S., Kobold S.: Killing mechanisms of chimeric antigen receptor (CAR) T cells. International Journal of Molecular Sciences, 2019, 20(6), 1283.
9. Maude S.L., Frey N., Shaw P.A., Aplenc R., Barrett D.M., Bunin N.J., Chew A., Gonzalez V.E., Zheng Z., Lacey S.F., Mahnke Y.D., Melenhorst J.J., Rheingold S.R., Shen A., Teachey D.T., Levine B.L., June C.H., Porter D.L., Grupp S A.: Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine, 2014, 371(16), 1507–1517.
10. Park J.H., Rivière I., Gonen M., Wang X., Sénéchal B., Curran K.J., Sauter C., Wang

Y., Santomasso B., Mead E., Roshal M., Maslak P., Davila M., Brentjens R. J., Sadelain M.: Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. The New England Journal of Medicine, 2018, 378(5), 449–459.

11. Santomasso B., Bachier C., Westin J., Rezvani K., Shpall E.J.: The other side of CAR T-cell therapy: cytokine release syndrome, neurologic toxicity, and financial burden. American Society of Clinical Oncology Educational Book, 2019, 39, 433–444.
12. Vormittag P., Gunn R., Ghorashian S., Veraitch F.S.: A guide to manufacturing CAR T cell therapies. Current Opinion in Biotechnology, 2018, 53, 164–181.
13. Hay K.A., Turtle C.J.: Chimeric antigen receptor (CAR) T cells: lessons learned from targeting of CD19 in B-cell malignancies. Drugs, 2017, 77(3), 237–245.
14. Levine B.L.: Performance-enhancing drugs: design and production of redirected chimeric antigen receptor (CAR) T cells. Cancer Gene Therapy, 2015, 22(2), 79–84.
15. Zhang H., Zhao P., Huang H.: Engineering better chimeric antigen receptor T cells. Experimental Hematology & Oncology, 2020, 9(1), 1–13.
16. Levine B.L., Miskin J., Wonnacott K., Keir C.: Global manufacturing of CAR T cell therapy. Molecular Therapy. Methods & Clinical Development, 2017, 4, 92–101.
17. Zabel M., Tauber P.A., Pickl W.F.: The making and function of CAR cells. Immunology Letters, 2019, 212, 53–69.
18. Jayaraman J., Mellody M.P., Hou A.J., Desai R.P., Fung A.W., Pham A.H.T., Chen Y.Y., Zhao W.: CAR-T design: Elements and their synergistic function. EBioMedicine, 2020, 58, 102931.
19. Huang R., Li X., He Y., Zhu W., Gao L., Liu Y., Gao L., Wen Q., Zhong J.F., Zhang C., Zhang X.: Recent advances in CAR-T cell engineering. Journal of Hematology & Oncology, 2020, 13(1), 1-9.
20. Weinkove R., George P., Dasyam N., McLellan A. D.: Selecting costimulatory domains for chimeric antigen receptors: functional and clinical considerations. Clinical & Translational Immunology, 2019, 8(5), e1049.
21. Wei J., Han X., Bo J., Han W.: Target selection for CAR-T therapy. Journal of Hematology & Oncology, 2019, 12(1), 1–9.
22. Pehlivan K.C., Duncan B.B., Lee D.W.: CAR-T cell therapy for acute lymphoblastic leukemia: transforming the treatment of relapsed and refractory disease. Current Hematologic Malignancy Reports, 2018, 13(5), 396–406.

23. Turtle C.J., Hanafi L.A., Berger C., Gooley T.A., Cherian S., Hudecek M., Sommermeyer D., Melville K., Pender B., Budiarto T.M., Robinson E.: CD19 CAR–T cells of defined CD4+: CD8+ composition in adult B cell ALL patients. The Journal of clinical investigation, 2016, 126(6), 2123-2138.
24. Xu X., Sun Q., Liang X., Chen Z., Zhang X., Zhou X., Li M., Tu H., Liu Y.U., Tu S., Li Y.: Mechanisms of relapse after CD19 CAR T-cell therapy for acute lymphoblastic leukemia and its prevention and treatment strategies. Frontiers in immunology, 2019, 10, 2664.
25. Song E.Z., Milone M.C.: Pharmacology of Chimeric Antigen Receptor – Modified T Cells. Annual Review of Pharmacology and Toxicology, 2021, 61, 805–829.
26. Zhang T., Cao L., Xie J., Shi N., Zhang Z., Luo Z., Yue D., Zhang Z., Wang L., Han W., Xu Z.: Efficiency of CD19 chimeric antigen receptor-modified T cells for treatment of B cell malignancies in phase I clinical trials: a meta-analysis. Oncotarget, 2015, 32, 33961.
27. Bachmann M.: The UniCAR system: a modular CAR T cell approach to improve the safety of CAR T cells. Immunology Letters, 2019, 211, 13–22.
28. Namuduri M., Brentjens R. J.: Medical management of side effects related to CAR T cell therapy in hematologic malignancies. Expert Review of Hematology, 2016, 9(6), 511–513.
29. Elahi R., Khosh E., Tahmasebi S., Esmaeilzadeh A.: Immune cell hacking: challenges and clinical approaches to create smarter generations of chimeric antigen receptor T cells. Frontiers in Immunology, 2018, 9, 1717.
30. Zhang C., Durer S., Kasi A.: Chimeric Antigen Receptor (CAR) T-Cell Therapy. StatPearls Publishing, 2020.
31. Titov A., Petukhov A., Staliarova A., Motorin D., Bulatov E., Shuvalov O., Soond S.M., Piacentini M., Melino G., Zaritskey A., Barlev N.A.: The biological basis and clinical symptoms of CAR-T therapy-associated toxicites. Cell death & disease, 2018, 9(9), 1-5.
32. Kennedy V.E., Wong C., Huang C.Y., Wolf J.L., Martin T., Shah N., Wong S.W.: Macrophage activation syndrome-like manifestations (MAS-L) following BCMA-directed CAR T-cells in multiple myeloma. InBlood, 2021, 136.
33. Zhao Z., Chen Y., Francisco N. M., Zhang Y., Wu M.: The application of CAR-T cell

therapy in hematological malignancies: advantages and challenges. Acta Pharmaceutica Sinica B, 2018, 8(4), 539–551.

34. Mohanty R., Chowdhury C. R., Arega S., Sen P., Ganguly P., Ganguly N.: CAR T cell therapy: a new era for cancer treatment. Oncology Reports, 2019, 42(6), 2183–2195.
35. FDA's Product Information: Breyanzi (lisocabtagene maraleucel) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel (cited: 13.07.2021).
36. FDA's Product Information: Kymriah (tisagenlecleucel) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel (cited: 13.07.2021).
37. FDA's Product Information: Abecma (idecabtagene vicleucel) https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel (cited: 13.07.2021).
38. FDA's Product Information: Yescarta (axicabtagene ciloleucel) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (cited: 13.07.2021).
39. FDA's Product Information: Tecartus (brexucabtagene autoleucel) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel (cited: 13.07.2021).
40. European Medicines Agency' Product Information: Tecartus https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus (cited: 13.07.2021).
41. European Medicines Agency' Product Information: Yescarta https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta (cited: 13.07.2021).
42. European Medicines Agency' Product Information: Kymriah https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah (cited: 13.07.2021).
43. Mahadeo K.M., Khazal S.J., Abdel-Azim H., Fitzgerald J.C., Taraseviciute A., Bollard C.M., Tewari P., Duncan C., Traube C., McCall D., Steiner M.E.: Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nature Reviews Clinical Oncology, 2019, 16(1), 45-63.
44. Yakoub-Agha I., Chabannon C., Bader P., Basak G.W., Bonig H., Ciceri F., Corbacioglu S., Duarte R.F., Einsele H., Hudecek M., Kersten M.J.: Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice

recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica, 2020, 105(2), 297.

45. Maus M.V., Alexander S., Bishop M.R., Brudno J.N., Callahan C., Davila M.L., Diamonte C., Dietrich J., Fitzgerald J.C., Frigault M.J., Fry T.J., Holter-Chakrabarty J.L., Komanduri K.V., Lee D.W., Locke F.L., Maude S.L., McCarthy P.L., Mead E., Neelapu S.S., Neilan T.G., Santomasso B.D., Shpall E.J., Teachey D.T., Turtle C.J., Whitehead T., Grupp S.A.: Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. Journal for ImmunoTherapy of Cancer, 2020, 8(2), e001511.
46. Moreau P., Sonneveld P., Boccadoro M., Cook G., Mateos M.V., Nahi H., Goldschmidt H., Dimopoulos M.A., Lucio P., Bladé J., Delforge M.: Chimeric antigen receptor T-cell therapy for multiple myeloma: a consensus statement from The European Myeloma Network. Haematologica, 2019, 104(12), 2358.
47. Gupta R., Roach C., Hryniewicki A. T., Vilke G. M., Shatsky R. A., Coyne C. J., Management of Chimeric Antigen Receptor (CAR) T-Cell Toxicities: A Review and Guideline for Emergency Providers. Journal of Emergency Medicine, 2020, 59(1) 61–74.
48. No authors listed. CAR T-Cell Therapy Shows Durable Responses in Indolent NHL. Oncologist, 2020, 25(1), 6–7.
49. European Medicines Agency' Summary of opinion: Yescarta https://www.ema.europa.eu/en/documents/overview/yescarta-epar-medicine-overview_en.pdf (cited: 13. 07.2021).
50. Dreyling M., Ghielmini M., Rule S., Salles G., Ladetto M., Tonino S.H., Herfarth K., Seymour J.F., Jerkeman M.: Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 2021, 32(3), 298-308.
51. European Medicines Agency' Summary of opinion: Tecartus https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-tecartus_en.pdf (cited: 13.07.2021).
52. Clinicaltrials of Chimeric antigen receptor https://clinical trials.gov/ct2/results?term =CAR-T (cited: 13.07.2021).

New therapies for ovarian cancer

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Introduction

Ovarian cancer is the fifth [1] most common cancer affecting women and the eighth-most common cause of cancer death [2]. Unfortunately, there are no practical screening tools or specific symptoms occurring at the beginning of the disease. Therefore, the disease is recognized in an advanced stage, which increases mortality and morbidity [3.] The risk factors include family history of breast or ovarian cancer, high BMI, gonadotropic and steroid hormones, oncogenic and tumor suppressor genes, infertility. There are also factors like pregnancy, hysterectomy, tubal ligation, and oral contraceptives, which reduce ovarian cancer risk [1].

Primary treatment of newly diagnosed ovarian cancer includes surgical treatment and chemotherapy. The main aim of surgical treatment is the tumor's total cytoreduction; therefore, the operation is extensive: obtaining fluid for cytological study, bilateral salpingo-oophorectomy, radical hysterectomy, excision of the greater omentum, pelvic and aortic lymphadenectomy, and appendectomy are made. In addition, it is necessary for proper determination of the clinical stage. The standard chemotherapy protocol includes 3 to 6 cycles of platinum (carboplatin or cisplatin) and taxoid (paclitaxel) in 21-day cycles. Unfortunately, most patients are not sensitive to described first-line treatment, and the second-line chemotherapy protocol is needed.

The effect of first-line treatment defines the categories of patients:

- platinum-sensitive - recurrence after 12 months since completion of first-line treatment (33.5% of patients),
- partly platinum-sensitive - recurrence within 6-12 months after completion of first-line treatment (22.7% of patients),
- platinum-resistant - recurrence within six months after completion of first-line treatment (22.7% of patients).

- platinum non-sensitive - tumor progression during first-line treatment (5.3% of patients) [4].

In the second-line treatment, gemcitabine, doxorubicin, and other combinations are used [4], but still, the progression-free survival and overall survival are not satisfying; therefore, some other substances are needed.

Poly (ADP-ribose) polymerases (PARP)

Proteins belonging to the group of poly (ADP-ribose) polymerases (PARP) are responsible for identifying single-strand breaks in DNA and repairing them using base excision repair (BER) [5]. Impairment of the proper functioning of BER by PARP inhibitors (PARPi) leads to the formation of DNA double-strand breaks that cannot be repaired, for example, in cancer cells homozygous for the BRCA mutation. However, this process can occur without any problems in non-neoplastic BRCA carrier cells, which, due to their heterozygosity, ensure an adequate amount of functioning BRCA proteins [6]. On the other hand, sensitization of cells to PARPi by the presence of BRCA1 and BRCA2 dysfunction causes loss of chromosome stability, inhibition of the cell cycle, and apoptosis of neoplastic cells [7].

Niraparib is an inhibitor that is mainly directed against PARP-1 and PARP-2 [8]. In vitro, its activity against neoplastic cells was demonstrated regardless of BRCA1 and BRCA2 mutations [9]. In addition to the maintenance treatment of epithelial ovarian cancer, niraparib is approved to treat fallopian tube or primary peritoneal cancer in patients who have achieved a complete or partial response to platinum-containing chemotherapy [10]. The drug's efficacy was demonstrated by the randomized, double-blind, placebo-controlled phase III trial NOVA by Mirza et al. Patients in the study group with histologically confirmed serous ovarian cancer received 300 mg of niraparib daily in 28-day cycles. Among patients with the BRCA mutation, the study group had a longer progression-free time than the placebo group, 21.0 and 5.5 months, respectively (HR 0.27; 95% CI, 0.17 to 0.41). Among the most common adverse effects during the therapy there were: thrombocytopenia (33.8% of respondents), anemia (25.3%), and neutropenia (19.6%) [11].

Olaparib, also belonging to PARPi, effectively treats prostate, breast, and pancreatic cancers [12]. It has been approved in the United States and the European Union for maintenance therapy in advanced ovarian cancer, thanks to the results of the SOLO1 study. Patients with high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube

cancer with the BRCA1, BRCA2 mutation, or both, in whom response to platinum chemotherapy was partial or complete, have been included in the study. The study group received Olaparib at a dose of 300 mg twice a day, while the control group received a placebo. After approximately 41 months, the risk of disease progression or death in olaparib users was 70% lower than in controls. The clinically significant side effects associated with the therapy include, among others: nausea and anemia [13].

In combination with the anti-angiogenic bevacizumab, Olaparib is currently under consideration in patients with advanced ovarian cancer as first-line treatment [14].

The programmed death-1 receptor (PD-1), programmed death-ligand 1 (PD-L1)

The programmed death-1 receptor with its ligands, programmed death-ligand 1, and programmed death-ligand 2 play a role in inhibiting immune responses and promoting self-tolerance by modulating T-cell activity, which is essential in cancer immune escape and cancer treatment [15]. Its role was described in non-small cell lung cancer [16] and in ovarian, cervical, vulvar and uterine cancers [17]. Lin Wang's study contained 1630 ovarian cancers and analysed PD-L1 protein expression, which was not associated with tumor grade, clinical stage, lymph node status, tumor histology, overall survival (OS), and progression-free survival (PFS). However, the PD-L1 mRNA expression was linked with worse PFS in 1228 patients [18]. The other study showed that patients with higher PD-L1 expression had significantly worse overall survival (OS) and progression-free survival (PFS) compared with patients with lower PD-L1 expression [19]. Additionally, the connection between the presence of PD-1/PD-L1 on monocytes in the ascites and stages of cancer is also described. PD-L1 expression on monocytes was significantly higher in ovarian cancer than in benign or borderline tumors, suggesting that PD-L1 expression in the tumor environment is also important [20].

It is why the inhibition of PD-1/PD-L1 expression is expected to have promising efficacy in the treatment. It can be used in combination with other immune therapy or with chemotherapy. The monoclonal antibody binding to the PD-1 receptor is called nivolumab. It releases PD-1 pathway-mediated inhibition of immune response, owing to the antitumor response, including a possible decreased tumor growth. Twenty patients with platinum-resistant ovarian cancer were classified to phase II clinical study with nivolumab in the dose of 3-mg/kg. The median follow-up period was 11.0 months (3 to 32 months), and the duration of treatment

with nivolumab was 3.5 months (1 to 12 months). Serious adverse events, such as deep vein thrombosis or disorientation and gait disorder, were observed in two patients. 2 patients had the nivolumab administration interrupted because of treatment-related thyroiditis [21].

In the single-arm, phase 2 study, nivolumab was combined with bevacizumab in women with relapsed ovarian cancer. 18 out of 38 patients have been qualified as platinum-resistant and 20 - platinum-sensitive; they received medicaments every two weeks. Eleven women had confirmed a response to nivolumab and bevacizumab. The overall response rate (ORR) in the platinum-sensitive group was 40.0%, and in platinum-resistant participants - 16.7%. Median progression-free survival was 8.1 months [22].

Pembrolizumab, a monoclonal antibody to the PD-L1, was admitted in the dose of 10 mg/kg every two weeks to 26 patients with metastatic ovarian cancer in a multicohort, phase Ib trial. A mediad follow-up duration and a median progression-free survival were 15.4 months and 1.9 months, respectively. Nineteen patients had treatment-related adverse events, among which arthralgia, nausea, and pruritus were the most common [23].

TTFields and paclitaxel

Carboplatin might not be the only possible therapeutic option to accompany the paclitaxel treatment. Alternating electric field therapy, or tumour treating fields (TTFields), which is an antineoplastic therapeutic strategy utilising low-voltage (1-3V/cm of tissue), intermediate frequency (200 kHz) alternating electric fields, delivered locoregionally, was approved for central nervous system tumours by FDA in 2015 and is now considered a potential ovarian cancer therapy method. A randomized clinical trial conducted by Stupp et al. [24] showed a significantly longer progression-free period (HR=0.62, 98,7% CI=0.43-0.89) and overall better survival rate (HR=0.64; 99,4% CI=0.42-0.98) in 315 glioblastoma patients treated with temozolomide and TTFields versus 229 patients on temozolomide alone. Furthermore, combined therapy did not cause any negative influence on health-related quality of life compared to temozolomide alone, besides local skin itchiness due to the nature of TTFields and used transducer arrays [25].

Testing the possibility of using TTFields as an element of therapeutic strategy in ovarian cancer began right after the FDA approval of TTFields for glioblastoma treatment; in 2016, Voloshin *in vitro* and *in vivo* study [26]. The human ovarian cancer cells *in vitro* displayed a significant reduction of their quantity after being exposed to the TTFields, especially in

combination with paclitaxel. The effect was intensity- and frequency-dependent. The optimal frequency associated with the lowest amount of live cancer cells was 200 kHz. The test of combined treatment *in vivo* was conducted using a mice model with implanted MOSE-L_{TICv} cells. Tumours showed a significant reduction in their luminescence and weight. The initial results provided the necessary warranty for the analysis during the clinical trial. The INNOVATE (EF-22) phase I/II perspective, a single-arm, non-randomized, open-label pilot trial, was designed to study the safety and preliminary efficacy of TTF along with simultaneous weekly paclitaxel administration on the recurrent ovarian carcinoma. The results [27] included no serious adverse effects related to the TTFields besides dermatitis (84% of patients, only one patient discontinued therapy). In addition, 25% of patients displayed partial clinical response to the therapy, although the median overall survival was not reached. Due to the TTFields therapeutic potential and its non-invasive nature, it are expected to be a breakthrough in ovarian cancer treatment. Its efficacy in combination with paclitaxel in ovarian cancer is currently researched in phase 3 clinical trial, which is estimated to have been completed in September 2023 (ClinicalTrials.gov Identifier: NCT03940196).

Mirvetuximab soravtansine

One of the suggested therapeutic targets in ovarian cancer is folate receptor alpha (FRα), whose expression tends to be elevated in epithelial ovarian cancer. An antibody-drug conjugate mirvetuximab soravtansine (MIRV) utilises it by selectively binding the receptor and delivering maytansinoid DM4, a tubulin-targeting agent which induces mitotic arrest. After positive results of *in vitro* and *in vivo* animal studies [28] which revealed synergistic antiproliferative effects of the conjugate and carboplatin or doxorubicin in the IGROV-1 ovarian cancer cell line *in vitro*, and improved antineoplastic activity in xenograft mice models *in vivo* in both platinum-sensitive and resistant cell lines, several clinical trials began.

The objectives of phase 1 trials were to evaluate the safety, maximum dose, and preliminary efficacy of MIRV in various setups. The 2017 study [29] included patients with platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer and showed manageable safety profile in all patients and high antineoplastic activity in ovarian cancer. Authors of another 2017 study [30] obtained similar results in solid tumours patients, with the most pronounced antitumor activity in patients with ovarian cancer. A 2018 study [31] on MIRV in combination with carboplatin in patients with ovarian cancer, which was platinum-

sensitive, demonstrated good tolerance of the treatment as well as high activity against cancer. Similar results were published two years later [32] regarding MIRV combination with bevacizumab. Further analyses showed the possibility of identification of patients eligible for the treatment through FRα expression measurements.

Additionally, higher receptor expression turned out to be correlated with the more significant antineoplastic activity of MIRV [33]. After a promising phase, I studies, the first phase III study [34] did not reach the statistical significance regarding the primary endpoint, which was appropriate progression-free survival in the intention-to-treat and FRα high populations. However, the secondary endpoints, including objective response rate, overall survival, and patient-reported outcome, were met.

Currently, MIRV is designated as an orphan drug in Europe and in the US. It also received Fast Track designation for patients with a medium to high FRα-positive platinum-resistant ovarian cancer, after a minimum one, but a maximum of three prior systemic treatment series. However, as the primary endpoint had not been met during the first phase 3 clinical trial, the FDA has not granted accelerated approval for MIRV, although several phases 1, 2, and 3 clinical trials are currently underway.

Discussion

The typical first-line treatment of ovarian cancer does not have satisfying results. Therefore some new substances used in other types of cancer, like Olaparib, pembrolizumab, TTFields, or others described in our review, can be useful in ovarian cancer therapy. Especially in patients who are not sensitive to platinum, those therapies may be supportive and life-saving.

References

1. Salehi F., Dunfield L., Phillips K.P., Krewski D., Vanderhyden B.C.: Risk factors for ovarian cancer: an overview with emphasis on hormonal factors. Journal of Toxicology and Environmental Health Part B, Critical Reviews, 2008, 11(3–4), 301–21.
2. Webb P.M., Jordan S.J.: Epidemiology of epithelial ovarian cancer. Best Practice & Research Clinical Obstetrics & Gynaecology, 2017, 41, 3–14.
3. Rooth C.: Ovarian cancer: risk factors, treatment and management. British Journal of Nursing (Mark Allen Publishing), 2013, 22(17), S23-30.

4. Recommendation of the Polish Society of Oncological Gynaecology on the diagnosis and treatment of epithelial ovarian cancer | Basta | Oncology in Clinical Practice. https://journals.viamedica.pl/oncology_in_clinical_practice/article/view/44800/36018 [cited 2021 Jul 30].
5. Frampton J.E.: Olaparib: a review of its use as maintenance therapy in patients with ovarian cancer. BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy, 2015, 29(2), 143–50.
6. Basu B., Sandhu S.K., Bono J.S. de.: PARP inhibitors: mechanism of action and their potential role in the prevention and treatment of cancer. Drugs, 2012, 72(12), 1579–90.
7. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. https://pubmed.ncbi.nlm.nih.gov/15829967/ [cited 2021 Jul 30].
8. Heo Y.-A., Duggan S.T.: Niraparib: A Review in Ovarian Cancer. Targeted Oncology, 2018, 13(4), 533–9.
9. Zejula. European Medicines Agency. 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/zejula. [cited 2021 Jul 30].
10. Research C for DE and. Niraparib (ZEJULA). FDA. 2019 Sep 2. https://www.fda.gov/drugs/resources-information-approved-drugs/niraparib-zejula [cited 2021 Jul 30].
11. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. https://pubmed.ncbi.nlm.nih.gov/27717299/ [cited 2021 Jul 30].
12. DiSilvestro P., Colombo N., Scambia G., Kim B.-G., Oaknin A., Friedlander M., Lisyanskaya A., Floquet A., Leary A., Sonke G.S., Gourley C., Banerjee S., Oza A., González-Martín A., Aghajanian C.A., Bradley W.H., Mathews C.A. i wsp.: Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 2020, 38(30), 3528–37.
13. Moore K., Colombo N., Scambia G., Kim B.-G., Oaknin A., Friedlander M., Lisyanskaya A., Floquet A., Leary A., Sonke G.S., Gourley C., Banerjee S., Oza A., González-Martín A., Aghajanian C., Bradley W., Mathews C. i wsp.: Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. The New England Journal of Medicine, 2018, 379(26), 2495–505.
14. Ray-Coquard I., Pautier P., Pignata S., Pérol D., González-Martín A., Berger R., Fujiwara K., Vergote I., Colombo N., Mäenpää J., Selle F., Sehouli J., Lorusso D.,

15. Guerra Alía E.M., Reinthaller A., Nagao S., Lefeuvre-Plesse C. i wsp.: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. The New England Journal of Medicine, 2019, 381(25), 2416–28.
16. Schütz F., Stefanovic S., Mayer L., Au A. von., Domschke C., Sohn C.: PD-1/PD-L1 Pathway in Breast Cancer. Oncology Research and Treatment, 2017, 40(5), 294–7.
17. Xia L., Liu Y., Wang Y.: PD-1/PD-L1 Blockade Therapy in Advanced Non-Small-Cell Lung Cancer: Current Status and Future Directions. The Oncologist, 2019, 24(Suppl 1), S31–41.
18. The Controversial Role of PD-1 and Its Ligands in Gynecological Malignancies. https://pubmed.ncbi.nlm.nih.gov/31681606/ [cited 2021 Jul 30].
19. Wang L.: Prognostic effect of programmed death-ligand 1 (PD-L1) in ovarian cancer: a systematic review, meta-analysis and bioinformatics study. Journal of Ovarian Research, 2019, 12(1), 37.
20. Mandai M., Hamanishi J., Abiko K., Matsumura N., Baba T., Konishi I.: Anti-PD-L1/PD-1 immune therapies in ovarian cancer: basic mechanism and future clinical application. International Journal of Clinical Oncology, 2016, 21(3), 456–61.
21. Hamanishi J., Mandai M., Iwasaki M., Okazaki T., Tanaka Y., Yamaguchi K., Higuchi T., Yagi H., Takakura K., Minato N., Honjo T., Fujii S.: Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America, 2007, 104(9), 3360–5.
22. Hamanishi J., Mandai M., Ikeda T., Minami M., Kawaguchi A., Murayama T., Kanai M., Mori Y., Matsumoto S., Chikuma S., Matsumura N., Abiko K., Baba T., Yamaguchi K., Ueda A., Hosoe Y., Morita S. i wsp.: Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 2015, 33(34), 4015–22.
23. Liu J.F., Herold C., Gray K.P., Penson R.T., Horowitz N., Konstantinopoulos P.A., Castro C.M., Hill S.J., Curtis J., Luo W., Matulonis U.A., Cannistra S.A., Dizon D.S.: Assessment of Combined Nivolumab and Bevacizumab in Relapsed Ovarian Cancer: A Phase 2 Clinical Trial. JAMA oncology, 2019, 5(12), 1731–8.
24. Varga A., Piha-Paul S., Ott P.A., Mehnert J.M., Berton-Rigaud D., Morosky A., Yang P., Ruman J., Matei D.: Pembrolizumab in patients with programmed death ligand

1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. Gynecologic Oncology, 2019, 152(2), 243–50.

25. Stupp R., Taillibert S., Kanner A.A., Kesari S., Steinberg D.M., Toms S.A., Taylor L.P., Lieberman F., Silvani A., Fink K.L., Barnett G.H., Zhu J.-J., Henson J.W., Engelhard H.H., Chen T.C., Tran D.D., Sroubek J. i wsp.: Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA, 2015, 314(23), 2535–43.
26. Taphoorn M.J.B., Dirven L., Kanner A.A., Lavy-Shahaf G., Weinberg U., Taillibert S., Toms S.A., Honnorat J., Chen T.C., Sroubek J., David C., Idbaih A., Easaw J.C., Kim C.-Y., Bruna J., Hottinger A.F., Kew Y. i wsp.: Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma: A Secondary Analysis of a Randomized Clinical Trial. JAMA oncology, 2018, 4(4), 495–504.
27. Voloshin T., Munster M., Blatt R., Shteingauz A., Roberts P.C., Schmelz E.M., Giladi M., Schneiderman R.S., Zeevi E., Porat Y., Bomzon Z., Urman N., Itzhaki A., Cahal S., Kirson E.D., Weinberg U., Palti Y.: Alternating electric fields (TTFields) in combination with paclitaxel are therapeutically effective against ovarian cancer cells in vitro and in vivo. International Journal of Cancer, 2016, 139(12), 2850–8.
28. Vergote I., Moos R. von., Manso L., Van Nieuwenhuysen E., Concin N., Sessa C.: Tumor Treating Fields in combination with paclitaxel in recurrent ovarian carcinoma: Results of the INNOVATE pilot study. Gynecologic Oncology, 2018, 150(3), 471–7.
29. Ponte J.F., Ab O., Lanieri L., Lee J., Coccia J., Bartle L.M., Themeles M., Zhou Y., Pinkas J., Ruiz-Soto R.: Mirvetuximab Soravtansine (IMGN853), a Folate Receptor Alpha-Targeting Antibody-Drug Conjugate, Potentiates the Activity of Standard of Care Therapeutics in Ovarian Cancer Models. Neoplasia (New York, NY), 2016, 18(12), 775–84.
30. Moore K.N., Martin L.P., O'Malley D.M., Matulonis U.A., Konner J.A., Perez R.P., Bauer T.M., Ruiz-Soto R., Birrer M.J.: Safety and Activity of Mirvetuximab Soravtansine (IMGN853), a Folate Receptor Alpha-Targeting Antibody-Drug Conjugate, in Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: A Phase I Expansion Study. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 2017, 35(10), 1112–8.
31. Moore K.N., Borghaei H., O'Malley D.M., Jeong W., Seward S.M., Bauer T.M., Perez

R.P., Matulonis U.A., Running K.L., Zhang X., Ponte J.F., Ruiz-Soto R., Birrer M.J.: Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor α-targeting antibody-drug conjugate, in patients with solid tumors. Cancer, 2017, 123(16), 3080–7.

32. Moore K.N., O'Malley D.M., Vergote I., Martin L.P., Gonzalez-Martin A., Malek K., Birrer M.J.: Safety and activity findings from a phase 1b escalation study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin in patients with platinum-sensitive ovarian cancer. Gynecologic Oncology, 2018, 151(1), 46–52.
33. O'Malley D.M., Matulonis U.A., Birrer M.J., Castro C.M., Gilbert L., Vergote I., Martin L.P., Mantia-Smaldone G.M., Martin A.G., Bratos R., Penson R.T., Malek K., Moore K.N.: Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. Gynecologic Oncology, 2020, 157(2), 379–85.
34. Martin L.P., Konner J.A., Moore K.N., Seward S.M., Matulonis U.A., Perez R.P., Su Y., Berkenblit A., Ruiz-Soto R., Birrer M.J.: Characterization of folate receptor alpha (FRα) expression in archival tumor and biopsy samples from relapsed epithelial ovarian cancer patients: A phase I expansion study of the FRα-targeting antibody-drug conjugate mirvetuximab soravtansine. Gynecologic Oncology, 2017, 147(2), 402–7.
35. Moore K.N., Oza A.M., Colombo N., Oaknin A., Scambia G., Lorusso D., Konecny G.E., Banerjee S., Murphy C.G., Tanyi J.L., Hirte H., Konner J.A., Lim P.C., Prasad-Hayes M., Monk B.J., Pautier P., Wang J. i wsp.: Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 2021, 32(6), 757–65.

Advancing psychosocial care in the current approach to the cancer patient treatment – examination of importance of psychosocial care in the current approach to the cancer patient treatment

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History of the development of psychooncology

Concern for the psychological comfort of cancer patients has always been an informal part of healthcare. However, the non-medical aspects of care have not always been the subject of systematic attention or research, and the change of approach was made less than three decades ago. Since then, the psychological and social impact of cancer has been setting a new direction for research.

Interest in the psychosocial aspects of cancer has grown steadily along with the development of knowledge about cancer. The time of 1850-1900 was the beginning of the first anesthetic operations. Back then, the diagnosis of neoplasm meant inevitable death. The term "cancer" has not yet been used. From the 1930s, oncology knowledge began to spread among physicians, and the first federations focused on neoplasm-treatment began to appear. In the 1940s, the first chemotherapeutic drug was introduced into treatment. Folic acid was first used to treat leukemia. At the same time, both the use and availability of radiotherapy have gradually increased. These new standards and trends have triggered social optimism and revive the faith in curing neoplasms. In the 1950s, the first success of chemotherapy was achieved. The first patient was cured of neoplasia (choriocarcinoma) without surgery and radiotherapy. Meanwhile, the first research papers on the impact of a cancer diagnosis on the patients' mental health began to appear.

The 1960s was a time of consistent development and improvement of cancer therapies. In the United Kingdom, increased efforts have been made to provide more compassionate care to patients dying of cancer. Cicely Saunders created the first hospice(specialized facility) –

Christopher's. Hospice in London in 1967. This center focused on improving symptom control and palliative care for terminally ill patients, including cancer patients. In 1970, Swedish psychiatrist Feigenberg became interested in psychological care for patients at Radiumhemmet, Karolinska Institute in Stockholm. As a result, the Psychosomatic Department was established in 1970, becoming the Psychosocial Department. Finally, in 1992, increased interest in the psychological, social, and behavioral issues of cancer led to the emergence of a new subspecialty in oncology: psycho-oncology [1].

Since then, research in this field has aimed to increase our understanding of the interactions between changes in the body and their effects on the mind. Psycho-oncology challenges the mechanical view of cancer. A psychological-based therapeutic approach has become a key tool in the care of cancer patients since the 1990s, improving not only physical and psychiatric symptoms but also the quality of life. Therefore, psychological care and psychotherapy for cancer patients should become the standard [2].

Overview of the influence of cancer diagnosis and treatment in representational groups of patients

The influence of cancer diagnosis on patients presented on the example of ovarian cancer

Ovarian cancer is currently one of the most significant oncological challenges. It is often diagnosed at a high stage when the prognosis is usually wrong. It is related to non-specific clinical symptoms in the early stage of the disease, which lead to diagnostic difficulties and the lack of a specific screening test [3].

After diagnosis, many patients may experience severe fear and dread. Additionally, they may experience anxiety, powerlessness, as well as irritation, and anger. Some psychologists define the reaction to the diagnosis among cancer patients as Post-traumatic Stress Disorder (PTSD). It is related to the immediate life-threatening experience. PTSD occurs when feelings of danger and anxiety persist with the same strength or even more vigorous intensity for more than a month, and at the same time, cause significant mental and physical difficulties in personal or professional relationships. PTSD symptoms most often appear up to 3 months after the traumatic event [4].

Post-traumatic stress disorder can also occur during or after cancer treatment. It has been observed that due to the organ dysfunction in ovarian cancer, PTSD is more common in women aged 40-50 years, of reproductive age and who want to become pregnant [5]. Factors

predisposing to the development of PTSD in patients with ovarian cancer are the moment of diagnosis and confirmation of the diagnosis, diagnosis of advanced cancer stage, social and personal consequences of the disease, prolonged and painful examinations and procedures, long hospital stays, and cancer recurrence.

Other psychiatric disorders are more frequently observed in women suffering from ovarian cancer than in the general population, apart from post-traumatic stress disorder. Oncologists are challenging, especially as their symptoms may be masked or mixed with other symptoms typical of cancer itself. These disorders can be divided into maladaptive and neuropsychological (acute and chronic) disorders [6]. A maladaptive disorder is a depressive disorder that can manifest itself as a hyperactive, hypoactive, or masked disorder and an anxiety disorder.

Patients with depression developed as a result of cancer usually have more significant difficulties in making decisions. They tend to isolate themselves from the environment, which increases the risk of irregular appointments, not following medical recommendations, and thus decline doctor-patient cooperation (compliance). Among this group of patients, there is a decrease in motivation and sense of meaning. According to new research, the molecules produced by cancer cells may be directly involved in the occurrence of depression. Neoplastic cells secrete cytokines, e.g., IL-1β, IL-6, IL-10, and TNF-α, which affect the biochemical pathways of serotonin, a substance whose amount in the body is reduced in depressive disorders [7]. This sheds light on depression in the course of cancer and encourages further research.

Another important factor that should be taken into consideration in the management of patients diagnosed and treated with ovarian cancer is anxiety disorder. The moment of realization of the diagnosis, visualization of the later course of the disease (remission, potential relapse, progression, termination of causal treatment). They induce a sense of loss of safety in cancer patients, which causes an increased level of anxiety. It is worth keeping in mind that with time, especially with the start of oncological treatment, anxiety usually decreases. It may be a result of the feeling of restoring partial control over the situation, as well as ensuring a feeling of security from the doctor [8].

Anxiety disorders can be divided into paralysing anxiety, free-floating anxiety, and anxiety syndrome. Panic disorder is sudden and violent anxiety characterized by short duration and presence of vegetative symptoms such as pressure spikes, increased heart rate, and breathing, a feeling of tightness in the chest, and a feeling of sudden breathlessness. This poses a great threat to the health of the patient because it causes an additional, intense burden on the

weakened system. The anxiety syndrome covers not only the mental sphere but also the behavioral and the vegetative-somatic one. It is otherwise known as pathological anxiety because it exceeds the physiological response. Third, free-floating anxiety causes constant disorientation in everyday activities and loss of self-esteem. It affects the difficulty in falling asleep and the occurrence of symptoms from the vegetative system. Moreover, in addition to the anxiety mentioned above, patients may develop specific phobias that appear during medical procedures, i.e., claustrophobia during repeated CT or MRI examinations, fear of injections, etc.

The effects of experiencing fear are ambivalent. On the one hand, they can lead to destruction and breakdown of the lifeline. They were also supposed to have a positive aspect of mobilization to action (e.g., cooperation with medical staff, adherence to recommendations, keeping to the dates of examinations and controls, etc.). One of the interesting phenomena related to the experiencing of trauma is post-traumatic development [9]. As a result of the reformulation of the life goals caused by the cancer disease, the patients can start to feel mobilization, willing action aimed at recovery, mental strength, and determination. Such a constructive strategy of adaptation to the disease is described in psycho-oncology as a strategy of the "fighting spirit" [10]. In turn, the adaptive change named "the positive re-evaluation" is supplemented by process of changes in the current world view and involvement focused on the more fundamental matters [11]. The choice of a model of coping with the mental aspect of the disease is affected by: the advance of the disease during the treatment and the stage of cancer which was diagnosed.

Moreover, it is worth mentioning that the female gender is a risk factor for the development of anxiety disorders. The number of women diagnosed with anxiety disorders is greater than that of men. Therefore, it is important to pay special attention to the psychological support of women suffering from ovarian cancer. The second important fact is that depression and anxiety disorders are the most common comorbid mental disorders [12].

The impact of testicular cancer on men's mental health

Second cancer that relates to the fragile sphere of intimacy is men's gonadal tumor, i.e., testicular cancer. It is currently the second most common type of cancer diagnosed in men aged 15 to 35. The curability of those diseases is high and oscillates around 95% [13]. In Poland, an increase in the incidence of 5% is observed every year and even 7% among young men. As morbidity increases, mortality continues to decline [14]. Therefore the male population with

testicular cancer and that of cancer survivors is constantly increasing. Given this reason, the mental state of testicular cancer patients and cancer survivors is a noticeable and extremely important issue in modern psychology and oncology.

The treatment in patients diagnosed with testicular cancer may have some long-term effects that include infertility, cardiovascular diseases, respiratory failure, and persistent neurological disorders. These patients are also at higher risk of developing a secondary neoplastic disease [13]. The diagnosis itself and the prospect of complications can have a significant impact on the patient's mental health.

There have been numerous studies covering the topic of the mental health and health-related quality of life of patients with testicular cancer. The conclusions of these studies have shown that those patients much more often present mental and psychosocial disorders than physical ones. Patients who suffered from testicular cancer showed a higher level of depression, stress, and anxiety compared to the general population. However, they were not reflected in the stage of cancer but were dependent on factors such as the style of coping with stress or the level of social support the patient was given [15].

Studies have shown that the greater social support the patient received during treatment, the smaller the observed negative psychological effect of the disease were – these patients had lower levels of depression and stress [15].

Social support has the strongest correlation with the general mental and emotional state of patients (mental health-related quality of life), as it facilitates involvement in positive strategies of coping with stress.

Another very important element correlating with the level of stress is the patient's sexuality. Research has shown that of all the symptoms described in the QLQ-TC26 questionnaire, the diagnosis, and treatment of testicular cancer have the strongest negative impact on the sexual functioning of patients. Many of them show no interest in sexual activity, do not remain active and report that they are not able to talk to their loved ones about sex [15].

The reduced frequency of intercourse increases the level of stress and deteriorates the general mental and emotional state. It can be influenced by both problems with communication and the image of one's own body after treatment – especially invasive – orchiectomy. The patients' intimate relationships are also affected by their concerns about fertility. Patients with testicular cancer used fertility tests far more frequently and reported more difficulties in conceiving a child than in the general population [15].

When it comes to coping strategies, the strongest negative impact was observed in patients who perceived themselves to be guilty of the problems they encountered and who lost faith that they could cope with the disease and its complications (helpless style of coping) [15]. These patients showed a higher level of depression or stress. Such correlation is not unique to testicular cancer patients but has also been observed in other cancer patients.

The side effects of treatment also affect the level of anxiety and stress in testicular cancer patients [15]. Their intensification causes a deterioration of the mental state of patients, which may be related to the recalling of negative emotions that accompanied them during diagnosis and treatment. They often deteriorate the quality of life of patients and hinder functioning in everyday life.

A survey of patients who had undergone treatment due to testicular tumours was conducted. The results of the study showed a high percentage of patients who were in no way informed about the potential inconvenience related to mental health. Many patients were not warned about the emergence of stress, depression, or anxiety, even though most of them declared their willingness to educate and to accept psychological support [16]. Proper education would enable them to prepare for the treatment process as well as to seek specialistic help earlier.

It is extremely important to know what we can do to improve the mental state of patients suffering from testicular cancer and the survivors and thus increase their quality of life. Cognitive therapy turns out to be effective in changing the way patients deal with stress. Group therapy or attending support groups also achieve good results as they increase the level of psychological support [16].

Unfortunately, psychotherapy and seeking psychological help are still stigmatized, which may stop the patient from seeking specialistic help. Proposing online therapy is worth considering in that case, as it turns out to be as effective as therapy in the psychotherapeutic office [15].

Quality of life and mental health in paediatric cancer patients

After accidents, malignant neoplasms are the second most common cause of death among children [17].

Leukaemias are the most common childhood malignant neoplasms, while lymphomas and neoplasms of the central nervous system are ranked second and third, respectively [18].

The reasons for their development are not fully understood. Nevertheless, it is known that they are individually specific, and genetic predisposition, environmental factors, and comorbidities play a large role in their induction [19].

Diagnostic difficulties are caused, among others, by the rarity of cancer in children (1–1.5% of cancers in the entire population).

In Poland, this means the occurrence of about 1100–1200 new cases per year [20]. In European countries, there are about 35 thousand new cases of cancer every year among children, including 15,000 up to 14 years of age, and among adolescents and young adults aged 15-24, an additional 20,000 new cases [21].

It has been estimated that over the last 20 years, there has been a constant number of new cancer cases in the paediatric population [20].

Considerable advances in the treatment of paediatric cancers and the improvement of treatment conditions have resulted in the 5-year survival rate (OS-5) reaching almost 70% in children diagnosed with cancer [22]. When the disease is diagnosed, it is important to establish proper contact with the patient and his parents. Informing a child about their own health condition and diagnosis of the disease is a standard clinical procedure. The planned treatment regimen should be presented. There is also a need to disclose possible side effects and complications [23]. When intensive therapy is implemented, helping in order to achieve high survival results, the most common adverse effect is physical deterioration. The patient's physical condition deteriorates due to the side effects of the therapy. At the same time, the mental state of the patient worsens. It is related to increased dependence on adults, loss of control over life, and decreased participation in academic and extracurricular activities. This translates into a decreased sense of belonging to a community, changes in physical appearance, and problems in daily functioning. For those reasons, children with cancer have been identified as a group at risk of difficulties in psychosocial adjustment [24].

Identifying children who experience failure to adapt to the situation they have found themselves in because of a diagnosis of cancer is a clinical task that can have a large impact on treatment outcomes [25].

Numerous stressors related to cancer diagnosis and treatment may influence the development of abnormal adaptation mechanisms and poor functioning of children in various areas of life. Assessing cancer patients for problems in adjusting to the situation requires a multi-faceted approach. Screening children for difficulties in cognitive, behavioural, and affective functioning can help physicians decide if they need further evaluation and choose an

appropriate treatment regimen. Identifying factors associated with poor adjustment in children and adolescents with cancer may further facilitate the treatment of these children. That is why a multidisciplinary approach is so important [23,24].

The presence of psychologists, social workers, and psychiatrists in paediatric cancer departments raised awareness of the challenges faced by children with cancer. The introduction of psychological care into the standards of paediatric oncology centers allowed for appropriate education of patients on how to deal with isolation, hospitalization as well as pain and suffering associated with therapeutic procedures [25].

Several researchers have demonstrated in their clinical studies behavioural and emotional disorders in children treated for cancer, manifested by increased anxiety, depression, and withdrawal [24].

It has been shown that the risk of death in depressed cancer patients was 1.2 times higher than in patients without depression [26].

Moreover, difficulties in achieving mental well-being have been documented in children who also discontinued treatment [24].

The presence of specialized personnel helps in finding systemic solutions aimed at both parents and children. This helps in the functioning of the whole family, of which the child is an inseparable element [25].

In the multifaceted approach to the disease, the role of expert psychologists who would help families examine and deal with difficult problems is important. They would explain how to deal with difficult emotions related to diseases that threaten a child's life and future. Due to the young age of paediatric patients, the prospect of cancer-free adulthood differs significantly from that of their peers. Many forward-looking aspects are taken into account, the knowledge and understanding of which is necessary to plan the next course of action. Patients must be aware that the previous neoplastic treatment and possible co-occurring genetic defects and family conditions at a later time may affect the development of secondary neoplasms. Possible complications of intensive treatment, such as cardiotoxicity or endocrine disorders, which may result in the need to take medication for life, impaired daily functioning, or even disability, should also be taken into consideration [27].

An important aspect of future adult life is also the preservation of the child's fertility and the decision to freeze the germ cells [28].

The main goal of psycho-education and psychotherapy is to restore the psychosocial functioning of sick children. To normalize the patient's future life, efforts should be made to

educate both the child and his relatives [23].

The impact of cancer on the well-being and mental health of patients

For many patients, neoplastic disease is a very traumatic experience. Both the moment of diagnosis and the course of the disease may significantly affect and suddenly change the patient's lifestyle and quality of life. The studies carried out on the mentioned three groups of patients have shown the great impact on the mental health of the diagnosis of cancer. The diagnosis of a life-threatening disease, like cancer, maybe the cause of an acute stress reaction, which may even lead to the development of post-traumatic stress disorder or depressive disorders (29). Patients who have overcome their neoplastic disease have an over 1.5 times greater risk of developing post-traumatic stress disorder than the control group. Furthermore, relatives and caregivers of cancer survivors achieve similar results in their incidence of post-traumatic stress disorder [31]. The presented data on the risks associated with mental health in cancer patients suggest that every cancer patient should be covered by psychological care.

Cancer can significantly affect the patient's relationship with their body and their self-esteem. Exercise, appearance care, and positive thinking are recommended [29].

The help of psychologists and psychotherapists is essential for mental health. Decreased motivation of the cancer patients causes a worse response to rehabilitation and dietary advice. Therefore, proper attitude and psychological support are the basis for increasing the patient's well-being. Fear, anger, being out of control, and helplessness can get stronger with the progression of the disease. Consultation with the specialist seems to be key to finding appropriate forms of coping with emotions. Family and society also have a huge impact on the process, but in the case of the first group, awareness of the emotional strain on its members is necessary [30].

The feelings of anxiety and depression are more common in the patient's family members than in the control group. Lack of support from other relatives may even lead to suicidal thoughts in the caregivers. This is the reason why various types of aid programs, facilities allowing for finding an additional caregiver, flexibility of working hours, and understanding in the place of employment have significant importance [32].

Summarizing the results of all mentioned studies is no doubt that the psychological care offer for cancer patients and their families should be expanded. Thanks to this, the process of treating patients will be more holistic, according to the latest WHO definition of health,

describing health as a full physical, mental and social well-being, and not only the absence of disease or disability.

References

1. Holland J.C.: Psycho-oncology: Overview, obstacles, and opportunities. Psycho-oncology, 2018, 27(5), 1364-1376.
2. Lang-Rollin I., Berberich G.: Psycho-oncology. Dialogues in clinical neuroscience, 2018, 20(1), 13-22.
3. Blecharz P., Mądry R., Jasiówka M.: Treatment of advanced ovarian cancer with bevacizumab in Poland — a chance to improve survival still missed. Oncology in Clinical Practice, 2016, 12, 167–178.
4. Kieszkowska-Grudny A.: Zaburzenia psychiczne u chorych na nowotwory – podejście kliniczne. OncoReview , 2013, 3(2), 119-128.
5. Carter J., Raviv L., Applegarth L.: A cross-sectional study of the psychosexual impact of cancer-related infertility in women: third-party reproductive assistance. Journal of Cancer Survivorship, 2010, 4, 236–246.
6. Ducrocq F., Vaiva G., Cottencin O., Molenda S., Bailly D.: Post-traumatic stress, post-traumatic depression, and major depressive episode: literature. Encephale, 2001, 27(2), 159-68.
7. Pyter L.M., Pineros V., Galang J.A., McClintock M.K., Prendergast B.J.: Peripheral tumors induce depressive-like behaviors and cytokine production and alter hypothalamic-pituitary-adrenal axis regulation. Proceedings of the National Academy of Sciences, 2009, 106(22), 9069-9074.
8. Kieszkowska-Grudny A., Grudny J., Sierko E., Janowicz-Żebrowska A., Badurak P., Galar M., Wojtukiewicz M.Z.: Role of psychological and emotional factors in cancer related fatigue (CRF) syndrome in advanced NSCLC patients undergoing palliative chemotherapy. Advances in palliative medicine, 2010, 9(3), 81-86.
9. Tedeschi, R.G., Calhoun, L.G.: The Post-Traumatic Growth Inventory: Measuring the positive legacy of trauma. Journal of traumatic stress, 1996, 9(3), 455-471.
10. Juczyński Z.: Radzenie sobie ze stresem spowodowanym chorobą nowotworową. [w:] Psychoonkologia. de Walden-Gałuszko K. (red.). Wyd. Polskie Towarzystwo Psychiatryczne, Kraków, 2000.

11. Ogińska-Bulik N., Juczyński Z.: Rozwój potraumatyczny – charakterystyka i pomiar. Psychiatria, 2010, 7(4), 129-142.
12. Hirschfeld R.M.: The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. Prim Care Companion. Journal of Clinical Psychiatry, 2001, 3(6), 244-254.
13. Haugnes H.S., Bosl G.J., Boer H., Gietema J.A., Brydoy M., Oldenburg J., Dahl A.A., Bremnes R.M., Fossa S.D.: Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. Journal of Clinical Oncology, 2012, 30(30), 3752-3763.
14. Didkowska J., Wojciechowska U., Zatoński W.: Prognozy zachorowalności i umieralności na nowotwory złośliwe w Polsce do 2025 roku. Wydawnictwo Centrum Onkologii, Warszawa, 2009.
15. Butow P., Olver I., Luckett T., Grimison P., Toner G.C., Stockler M.R., Hovey E., Stubbs J., Turner S., Hruby G., Gurney H.: The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study. Journal of Cancer Survivorship, 2016, 10(2), 223-233.
16. Skoogh J., Steineck G., Johansson B., Wilderäng U., Stierner U.: Psychological needs when diagnosed with testicular cancer: findings from a population-based study with long-term follow-up. BJU International, 2013, 111(8), 1287-1293.
17. Hełka M., Musiał P., Stojko M., Moździerz A.: Nowotwory złośliwe u dzieci i młodzieży na terenie województwa śląskiego. Review and Research on Cancer Treatment, 2016, 2(1), 18-25.
18. Muszyńska-Rosłan K.: Jedne z najczęstszych nowotworów wieku dziecięcego – guzy mózgu i mięsaki tkanek miękkich. Opieka paliatywna nad dziećmi, 2009, 17, 149-153.
19. Wojciechowska U., Didkowska J., Michałek I., Olasek P., Ciuba A.: Nowotwory złośliwe w Polsce w 2018 roku. Wydawnictwo Centrum Onkologii, Warszawa 2020.
20. Balcerska A.: Epidemiologia chorób nowotworowych u dzieci. Forum Medycyny Rodzinnej, 2009, 3(1), 61–63.
21. Kowalczyk J.R.,: Epidemiologia nowotworów dziecięcych. [w:] Wprowadzenie do onkologii i hematologii dziecięcej. Kowalczyk J.R. (red.). Wyd. Centrum Medyczne Kształcenia Podyplomowego, Warszawa, 2011, 5-12.

22. Eiser Ch., Hill J.J., Vance Y.H.: Examining the Psychological Consequences of Surviving Childhood Cancer: Systematic Review as a Research Method in Pediatric Psychology. Journal of Pediatric Psychology, 2000, 25(6), 449–460.
23. Samardakiewicz M.R.: Psychologiczne aspekty choroby nowotworowej u dzieci. [w:] Wprowadzenie do onkologii i hematologii dziecięcej. Kowalczyk J.R. (red.). Wyd. Centrum medyczne kształcenia podyplomowego, Warszawa, 2011, 163-170.
24. Sanger M. S., Copeland D. R., Davidson E. R.: Psychosocial Adjustment Among Pediatric Cancer Patients: A Multidimensional Assessment. Journal of Pediatric Psychology, 1991, 16(4), 463-474.
25. Patenaude A.F., Kupst M.J.: Psychosocial Functioning in Pediatric Cancer. Journal of Pediatric Psychology, 2005, 30(1), 9-27.
26. Gołota Sz., Białczyk K., Wyszkowska Z., Popiołek A., Krajnik M., Borkowska A.: Lęk i depresja u chorych na nowotwory — co tracimy? Medycyna Paliatywna w Praktyce, 2017, 11(3), 111-117.
27. Stachowicz-Stencel T., Stefanowicz J., Bień E., Balcerska A.: Odległe następstwa leczenia nowotworów złośliwych u dzieci. Forum Medycyny Rodzinnej, 2009, 3(6), 485–493.
28. Takae S., Lee J.R., Mahajan N., Wiweko B., Sukcharoen N., Novero V., Anazodo A.C., Gook D., Tzeng C.R., Doo A.K., Li W.: Fertility preservation for child and adolescent cancer patients in Asian countries. Frontiers in endocrinology, 2019, 10, 655.
29. Bahrami M., Mohamadirizi M., Mohamadirizi S., Hosseini S.A.: Evaluation of body image in cancer patients and its association with clinical variables. Journal of education and health promotion, 2017, 6.
30. Fekete A., Fekete Z.: The psychologist role in oncology. Journal of Radiotherapy and Medical Oncology, 2012, 18(1), 27-29.
31. Im Song J., Shin D.W., Choi J.Y., Kang J., Baik Y.J., Mo H., Park M.H., Choi S.E., Kwak J.H., Kim E.J.: Quality of life and mental health in family caregivers of patients with terminal cancer. Supportive Care in Cancer, 2011, 19(10), 1519-1526.

Ischemic stroke prevention

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Introduction

Health prophylaxis is the most effective way to reduce the incidence of diseases. The knowledge of factors predisposing to the increase in the incidence of a given disease directs/defines the activities aimed at maintaining health. There are modifiable (human-dependent) and non-modifiable factors (not human-dependent, e.g. age, gender, race) [1].

The WHO (World Health Organization) reports that about 15 million people suffer from a stroke every year. The most common stroke is ischemic (incidence 70-80%), while 20-30% of the occurring strokes are hemorrhagic strokes. Subarachnoid hemorrhage (SAH) accounts for 5-7% of all strokes. The venous stroke is the least common as its incidence is 1-5 / 1000 strokes [2]. Death due to stroke is reported in 5.5 million of the world's population [3]. It is also the leading cause of disability (50% of patients diagnosed with stroke) and the second cause of dementia (25% of patients suffering from a stroke). After heart disease and cancer, it is the leading cause of death among the population of highly developed countries [3,4]. The likelihood of developing a stroke increases with age. The literature reports that after 55 years of age, it increases by 50% in the next ten years of life [5].

In people aged 35 - 44, the incidence of stroke ranges from 30 to 120 per 100,000 people per year, at the age of 55-64 the first episode happens in 300 / 100,000, while for the population aged 65 to 74 years, 670 - 970/100,000 people per year [3,6]. In children, a stroke occurs with a frequency of 2.5-2.7 in 100,000 people per year and usually affects boys up to 6 years of age. Under 18 years of age, ischemic stroke is less common than hemorrhagic stroke, accounting for 30-45% of cases [7].

The INTERSTROKE study including 13,447 strokes and an adequate number of

controls, conducted in 32 middle-income and low-income countries, showed that approximately 90% of strokes involve 10 modifiable risk factors [8]:

1) hypertension,
2) diabetes,
3) heart causes,
4) smoking tobacco,
5) abdominal obesity,
6) hyperlipidemia,
7) lack of physical activity,
8) alcohol consumption,
9) diet,
10) psychosocial stress and depression.

BMI (Body Mass Index) is an indicator of stroke predisposition which is independent of the effects of hypertension, diabetes, and cholesterol. As BMI is a modifiable risk factor, preventing stroke may be another benefit of treating obesity. Bodyweight shows a relationship directly proportional to the occurrence of ischemic episodes of the heart and brain. In addition, it has an affinity to other factors leading to stroke, including hypertension and diabetes. However, the data on the overall association of obesity and stroke and the subtypes of stroke are limited and inconclusive [9].

Diabetes is considered to be an independent factor of stroke, which is underestimated in diagnostics [10]. The literature shows that the mortality of patients with type II diabetes aged 45+ increases 6-8 times and by 12 times in hypertension. Moreover, it is emphasized that people with diabetes are twice as likely to develop atherosclerosis, which directly contributes to thromboembolic stroke [10].

Too numerous blood clotting factors can cause an ischemic stroke of thrombotic origin. In order to determine the efficiency of the coagulation system, the prothrombin time (PT) is used [11]. However, when it is incorrectly selected or conducted, oral contraception affects the thickness of the blood and may lead to thrombosis [12].

Hemorrhagic stroke may be caused by too high an INR (international normalized ratio) value [12]. Therefore, considering the above, people taking preparations that affect the coagulation system are at risk of suffering a stroke.

Cholesterol is a lipoprotein that is part of the cell membranes but is also responsible for the proper functioning of the circulatory system [13]. There are HDL and LDL fractions. HDL

(High-Density Lipoprotein) is high-density cholesterol and is colloquially called good cholesterol. Its main task is to transport fats from the peripheral tissues, which will be metabolized [14]. Normal HDL concentration in women should be above 50 mg/dl, and in men > 40g/dl [15]. The LDL (low-density lipoprotein) fraction is low-density cholesterol and is commonly known as bad cholesterol. The acceptable level of LDL is 115mg/dl (3.0 mmol/l) [15,16]. Its task is to transport fat particles to the peripheral cells [17]. Because it distributes lipids throughout the body, it causes plaque formation. The cholesterol level depends on, among others, physical activity and diet [18,19]. Dyslipidemia causes atherosclerosis, coronary artery disease, and stroke [13]. Triglycerides (TGs) are fat molecules that have two important functions in the human body. The first is providing energy for the body, while the second is storing fat molecules in the cytoplasm of the fat cell. Their level should not be higher than 150mg/dl (1.7mmol/l) [15,20]. The risk of an ischemic stroke is that fat cells aggregate on the atherosclerotic plaque, thereby reducing the lumen of a blood vessel. The final effect may be complete obstruction of the vessel or formation of a thrombus on the atherosclerotic plaque. An ischemic stroke occurs when a blood vessel closes, caused by a detached plaque or by a blood clot formed on its surface.

Methods

The author's stroke prevention program consisted of introducing dietary changes, health education, and an increase in the respondents' physical activity.

The survey has been running since January 2020. At quarterly intervals, blood pressure, glucose level, total cholesterol and its fractions, triglycerides, sodium and potassium levels, prothrombin time (PT), INR, PT activity were measured in each person included in the study. The exclusion criteria were not applied. The inclusion criterion was age, gender, consent to participate in the study, residence in the studied commune/town.

The study group consisted of 40 randomly selected women (the test and control group included 20 women each) aged 40-60 years from the Michałowo Community in Białystok district, who had an equal economic and social status. The project was financed from public funds as part of statutory work No. N/ST/MN/18/003/3310.

Additionally, an interview was collected to complete the proprietary questionnaire created based on the SF-36 Life Quality Assessment Questionnaire - Polish version. Finally,

statistical analysis was performed based on the Shapiro-Wilk distribution normality test and the t-student probability test. The above analyzes were performed in the Statistics program, version 13.3. The analysis performed is a sample, and it is recommended to repeat the study on a large population.

Results

During the stroke prevention program, the experimental group showed a statistically significant decrease in BMI values. Table 1 below presents the data obtained with the correlation between the measurements.

Table 1. Correlation of BMI values between the measurements in the experimental group

	GROUP=1 Test T for dependent test The differences marked are significant with p < ,0500									
Variable	Mean	Standard Deviation	Important	Difference	Standard Deviation, difference	t	df	p	Confidence -95%	Confidence +95%
BMI 0	29.7110	4.3168								
BMI 1	28.1398	3.2683	20	1.5711	1.4351	4.8959	19	0.0001	-2.2427	-0.8994
BMI 0	29.7110	4.3168								
BMI 2	26.7068	2.6023	20	3.0041	2.1997	6.1074	19	0.0000	-4.0336	-1.9746
BMI 0	29.7110	4.3168								
BMI 3	25.4481	2.0149	20	4.2628	2.6948	7.0742	19	0.0000	-5.5240	-3.0016
BMI 1	28.1398	3.2683								
BMI 2	26.7068	2.6023	20	1.4330	1.0886	5.8866	19	0.0000	-1.9425	-0.9235
BMI 1	28.1398	3.2683								
BMI 3	25.4481	2.0149	20	2.6917	1.5573	7.7296	19	0.0000	-3.4206	-1.9628
BMI 2	26.7068	2.6023								
BMI 3	25.4481	2.0149	20	1.2587	0.8594	6.5495	19	0.0000	-1.6609	-0.8564

BMI0 - measurement before the implementation of the prevention program; BMI1-3- measurements at 3-month intervals

The control group showed no statistically significant changes. Table 2 below presents the data obtained.

The above data are presented in the form of histograms (Figs. 1 and 2). In the test group, both the body weight and the deviation from the mean value decreased. In the control group, the graphs overlap, and no significant changes can be seen.

Another positive result of the health prophylaxis was an increase in HDL value and a reduction in LDL. LDL values dropped significantly in the experimental group. However, in the control group, they remained at a similar level or slightly increased in most cases.

The graphs below (Figs. 3 and 4) present the individual test results. Additionally, the threshold of the maximum acceptable value is marked. LDL0 - measurement before the implementation of the prevention program; LDL1-3- measurements at 3-month intervals.

Table 2. Correlation of BMI values between measurements in the control group

Variable	GROUP=2 Test T for dependent test The differences marked are significant with p < ,0500 Mean	Standard Deviation	Important	Difference	Standard Deviation, difference	t	df	p	Confidance -95%	Confidance +95%
BMI 0	27.0517	5.8633								
BMI 1	27.2559	5.9013	20	-0.2042	0.6448	-1.4161	19	0.1727	-0.0975	0.5060
BMI 0	27.0517	5.8633								
BMI 2	27.3396	5.5406	20	-0.2878	1.0797	-1.1923	19	0.2478	-0.2174	0.7932
BMI 0	27.0517	5.8633								
BMI 3	27.5995	5.7843	20	-0.5477	1.2299	-1.9917	19	0.0609	-0.0278	1.1234
BMI 1	27.2559	5.9013								
BMI 2	27.3396	5.5406	20	-0.0836	0.7709	-0.4850	19	0.6331	-0.277	0.4444
BMI 1	27.2559	5.9013								
BMI 3	27.5995	5.7843	20	-0.3435	0.9076	-1.6926	19	0.1068	-0.0815	0.7683
BMI 2	27.3396	5.5406								
BMI 3	27.5995	5.7843	20	-0.2599	0.9011	-1.2898	19	0.2125	-0.1618	0.6816

BMI0 - measurement before the implementation of the prevention program; BMI1-3- measurements at 3-month intervals

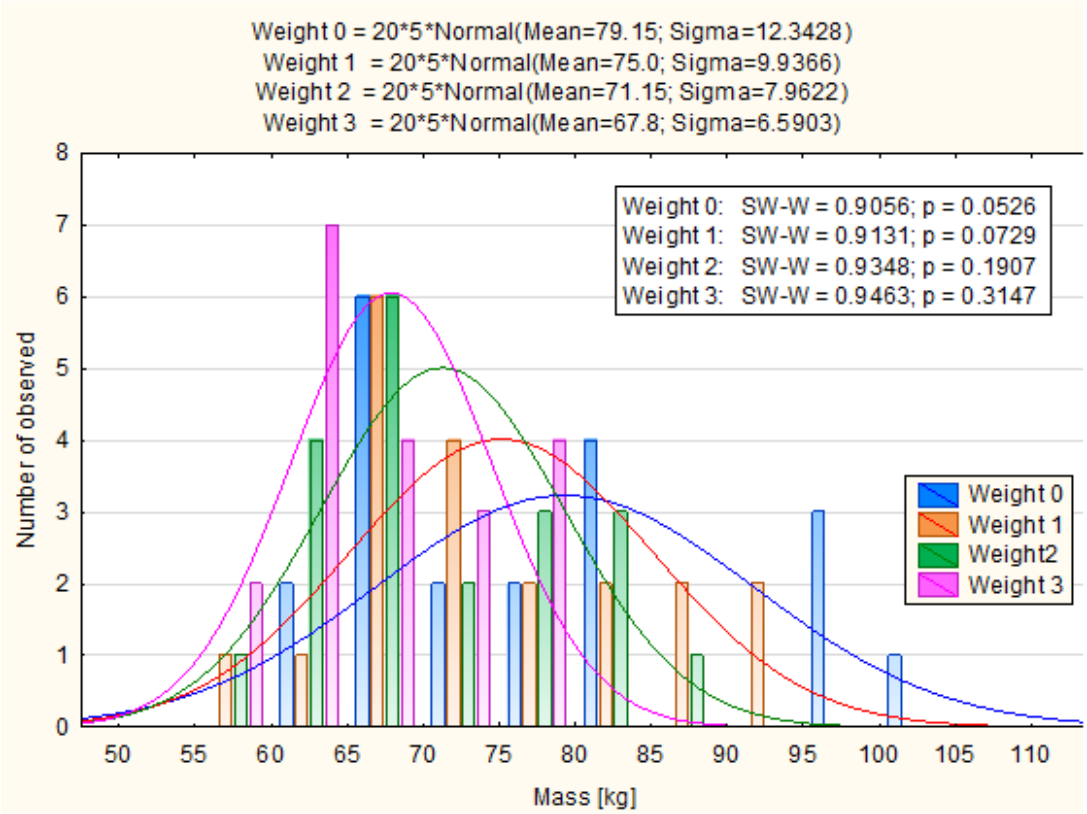


Figure 1. Graph of body weight in the experimental group over the period of 9 months

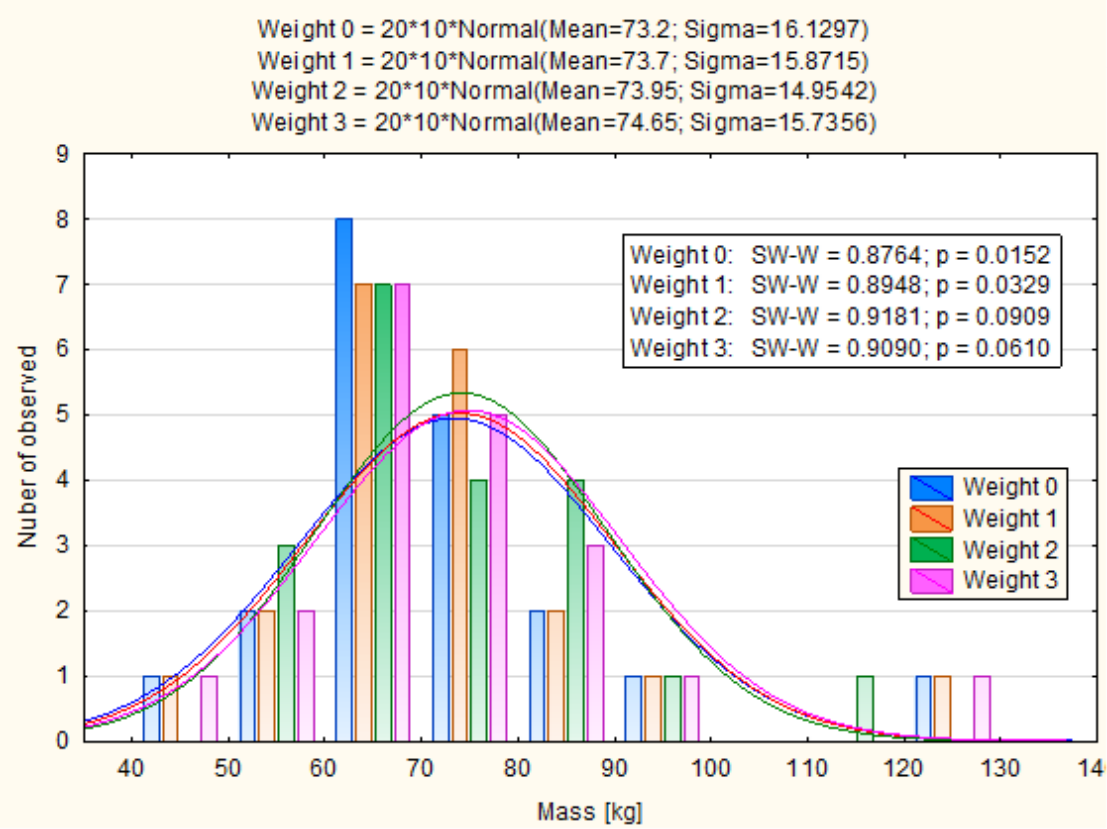


Figure 2. Graph of body weight in the control group over the period of 9 months

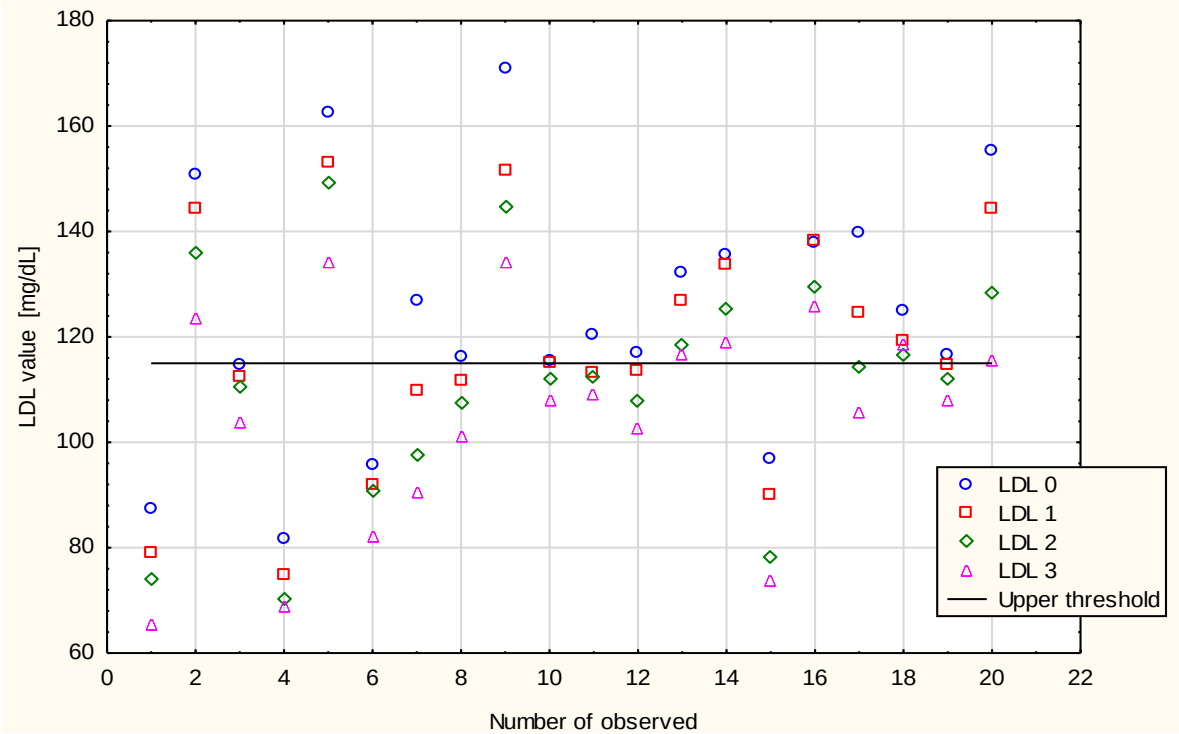


Figure 3. LDL value in the experimental group over the period of 9 months

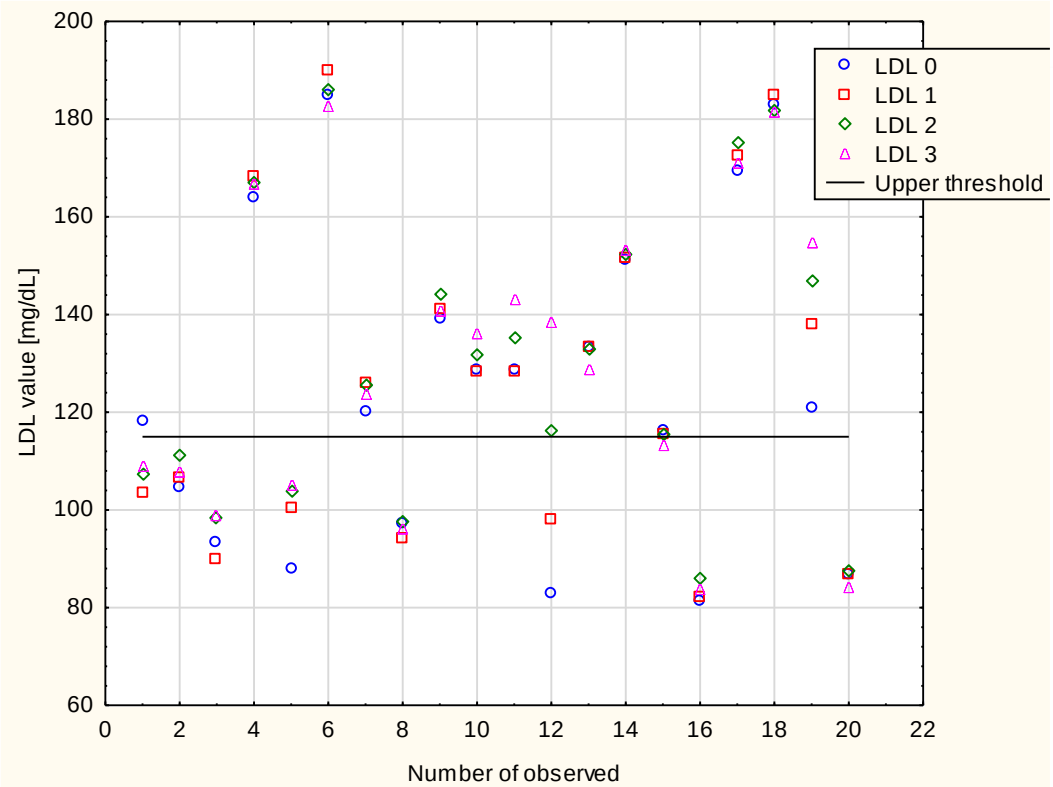


Figure 4. LDL value in the control group over the 9-month period

The HDL values were proportionally related to the LDL values, i.e., they increased in the experimental group and decreased in the control group. In order to observe the 9-month change, the data obtained are presented in the diagram. HDL0 - measurement before the implementation of the prevention program; HDL1-3- measurements at 3-month intervals.

The value of triglycerides is one of the assessments of atherosclerosis risk in the form of atherosclerotic plaques. The TG values are shown in the charts below- fig. 7 and fig.8. It can be observed that they did not change statistically significantly over the nine months. TG0 - measurement before the implementation of the prevention program; TG1-3- measurements at 3-month intervals.

The values of blood clotting indices did not change statistically significantly in the study group and in the control group during the entire study. The results were within the range of normal values for healthy people.

Moreover, correlations between the increase in the blood glucose level and the increase in body weight were observed at the significance level of $p < 0.05$. The graph below (Fig. 9) illustrates the quarterly change in blood glucose in the experimental group.

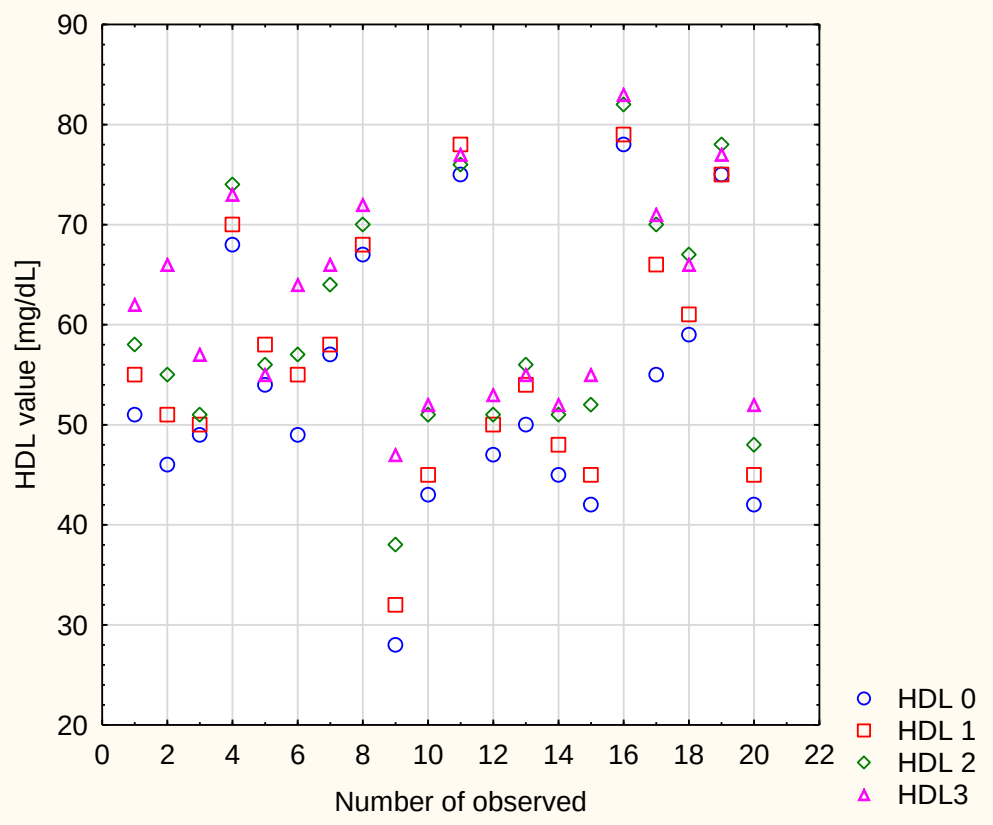


Figure 5. HDL value in the experimental group over the period of 9 months

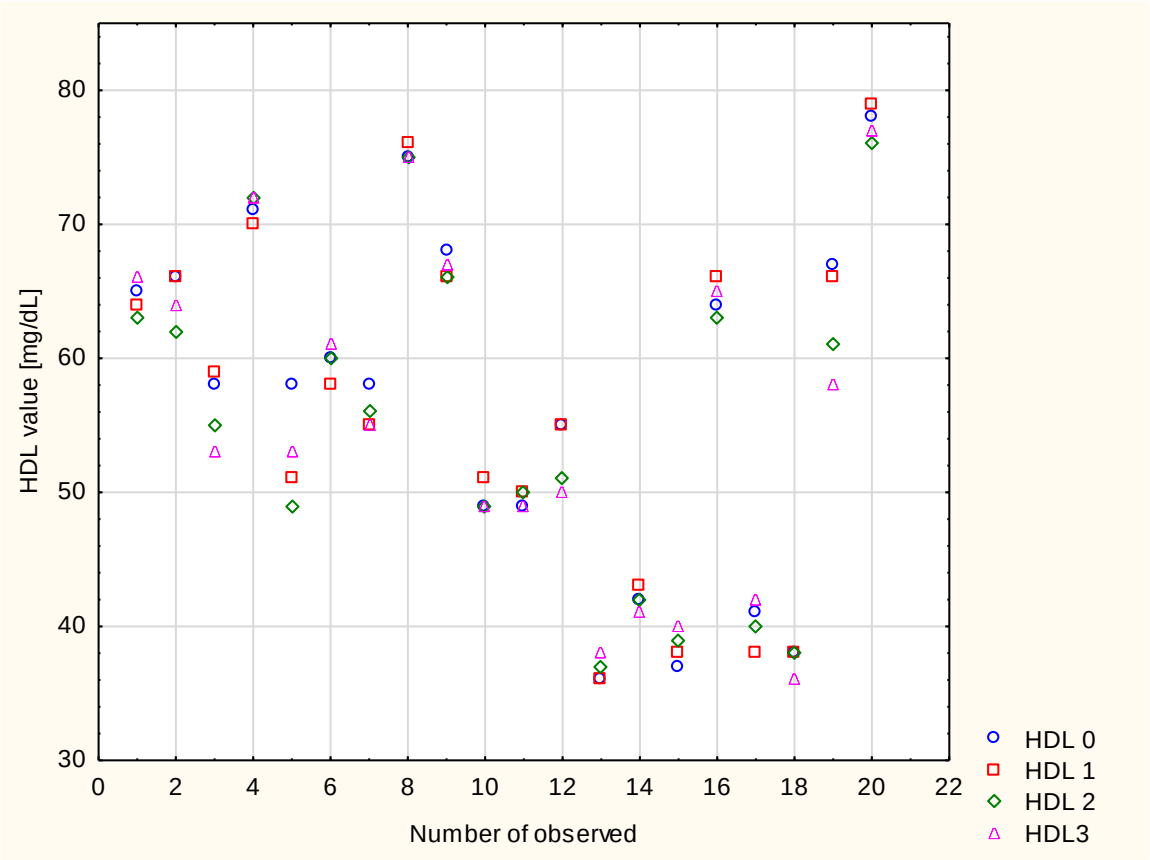


Figure 6. HDL value in the control group over 9 months

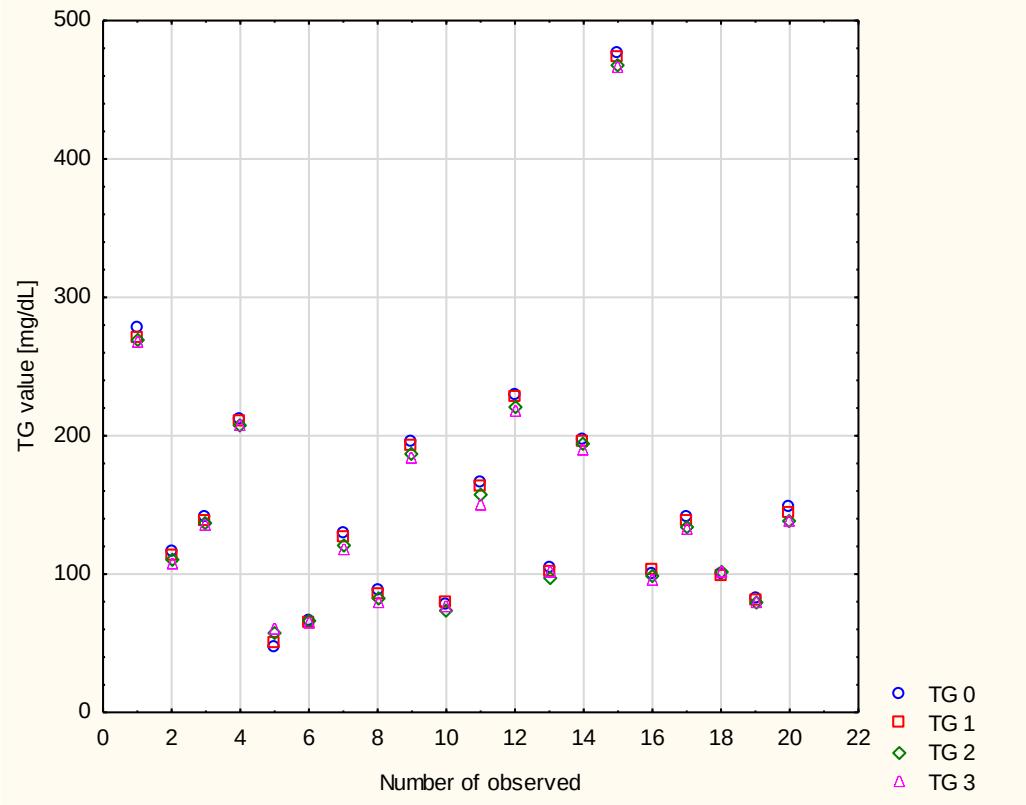


Figure 7. The value of TG in the experimental group over the period of 9 months

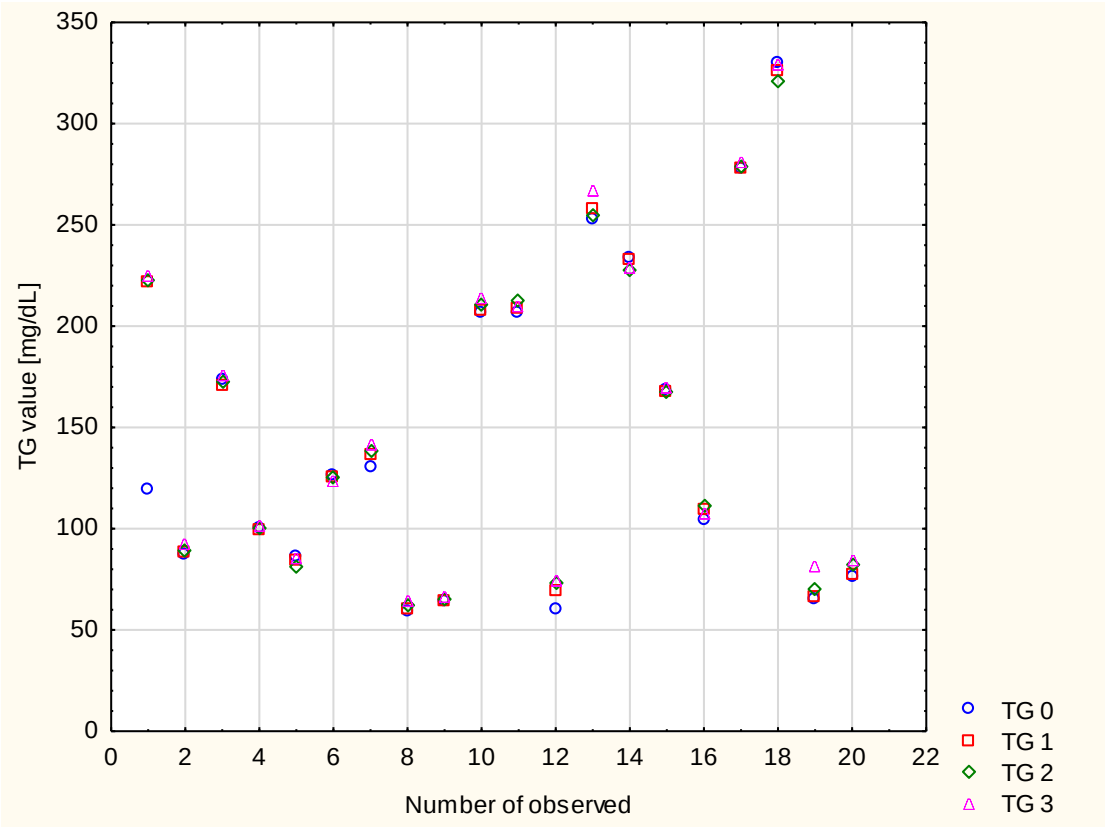


Figure 8. The value of TG in the control group over the period of 9 months

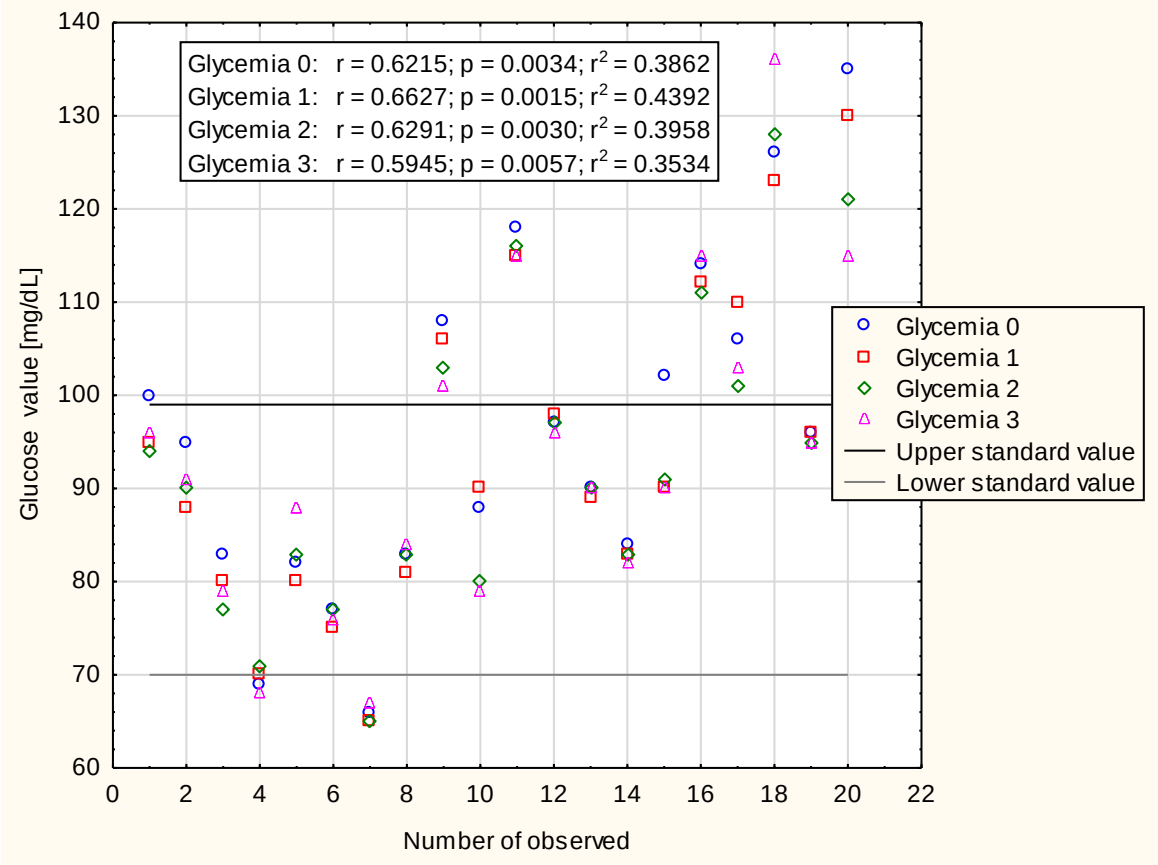


Figure 9. Fasting blood glucose levels in the experimental group over the 9-month period

Table 3 below shows the lack of a statistically significant correlation between blood glucose levels and body weight.

Table 3. Correlation of blood glucose values and body weight in the experimental group at quarterly intervals

	The marked correlation coefficients are statistically significant at p<.050			
Variable	Weight 0	Weight 1	Weight 2	Weight 3
Glycemia 0	0.0436	0.0628	0.0287	0.0358
Glycemia 1	0.0510	0.0638	0.0178	0.0309
Glycemia 2	0.0141	0.0104	-0.0238	-0.0127
Glycemia 3	-0.0068	-0.0201	-0.0334	-0.0104

Different values were obtained in the control group. The obtained data are presented below - Fig. 10, Tab. 4.

The value of systolic and diastolic pressure was analyzed. In the experimental group, most of the respondents reported a significant decrease in the values of systolic and diastolic

blood pressure. However, five patients had an increase in systolic blood pressure (by a maximum of 10%) after three months, regardless of the diastolic pressure value. In most cases in the control group, an increase systolic (up to 20%) and diastolic (up to 25%) pressure was found.. Graphs (Fig. 11-14) illustrating the data obtained are presented below.

It is worth underlying that the correlation between the increase in the systolic to diastolic pressure in both groups is statistically significant at the level of $p < 0.05$.

The obtained data divided into the study and control group were distributed as follows:

- Study group: systolic0: diastolic0: 0.6569; systolic1: diastolic1: 0.6375; systolic2: diastolic2: 0.5818; systolic3: diastolic3: 0.4963
- Control group: systolic0: diastolic0: 0.9218; systolic1: diastolic1: 0.8981; systolic2: diastolic2: 0.9186; systolic3: diastolic3: 0.8707.

It was checked whether there was a correlation between the change in the systolic blood pressure value and the level of weight loss during each control. The data obtained showed no statistically significant ($p > 0,05$) relationship in the value of body weight and systolic pressure in the experimental group: weight0: systolic0 -> 0.1826; mass1: systolic1 → 0.1420; mass2: systolic2 -> 0.0831; mass3: systolic3 -> - 0.0168.

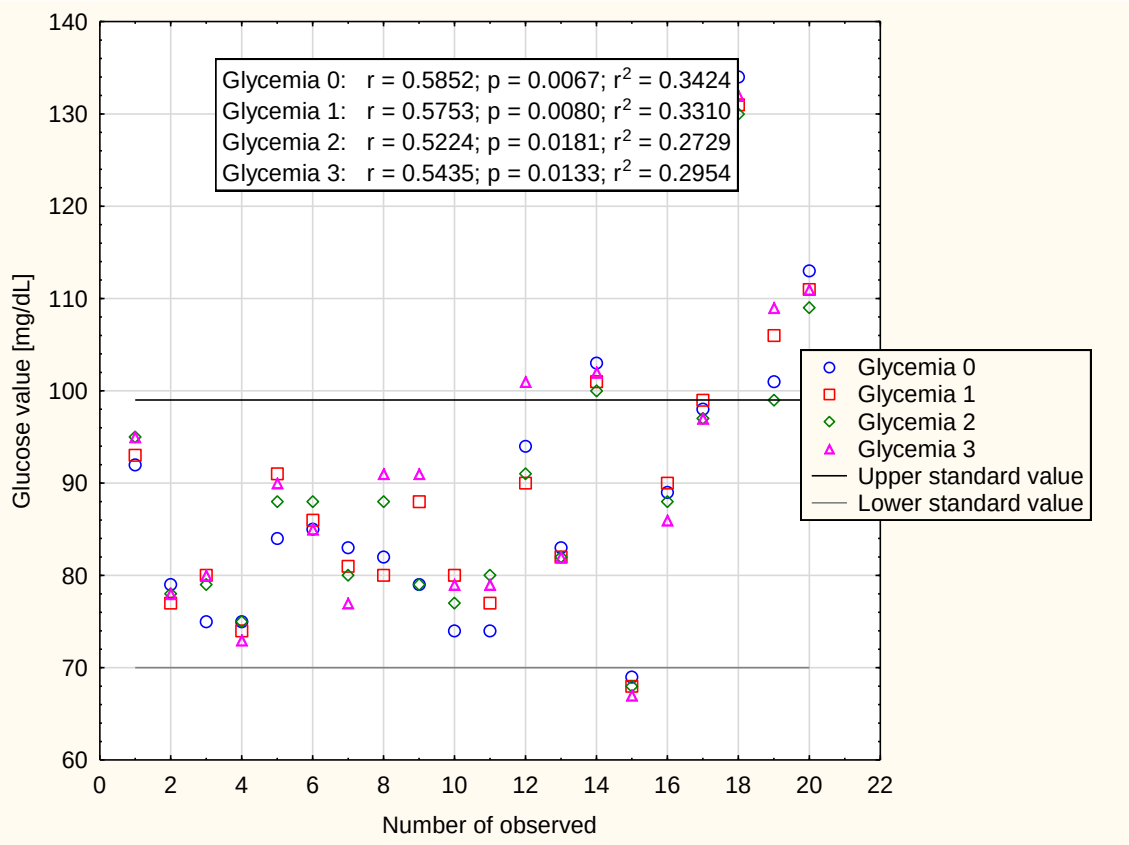


Figure 10. 9-month fasting glucose level in the control group

Table 4. Correlation of blood glucose values and body weight in the control group at quarterly intervals the marked correlation coefficients are significant at p<.05000 variable Mass 0, Mass 1, Mass 2, Mass 3

	The marked correlation coefficients are statistically significant at p<.0500			
Variable	Weight 0	Weight 1	Weight 2	Weight 3
Glycemia 0	0.5159	0.5071	0.4869	0.5144
Glycemia 1	0.4605	0.4560	0.4485	0.4693
Glycemia 2	0.5207	0.5106	0.4916	0.5216
Glycemia 3	0.3955	0.3890	0.3730	0.4227

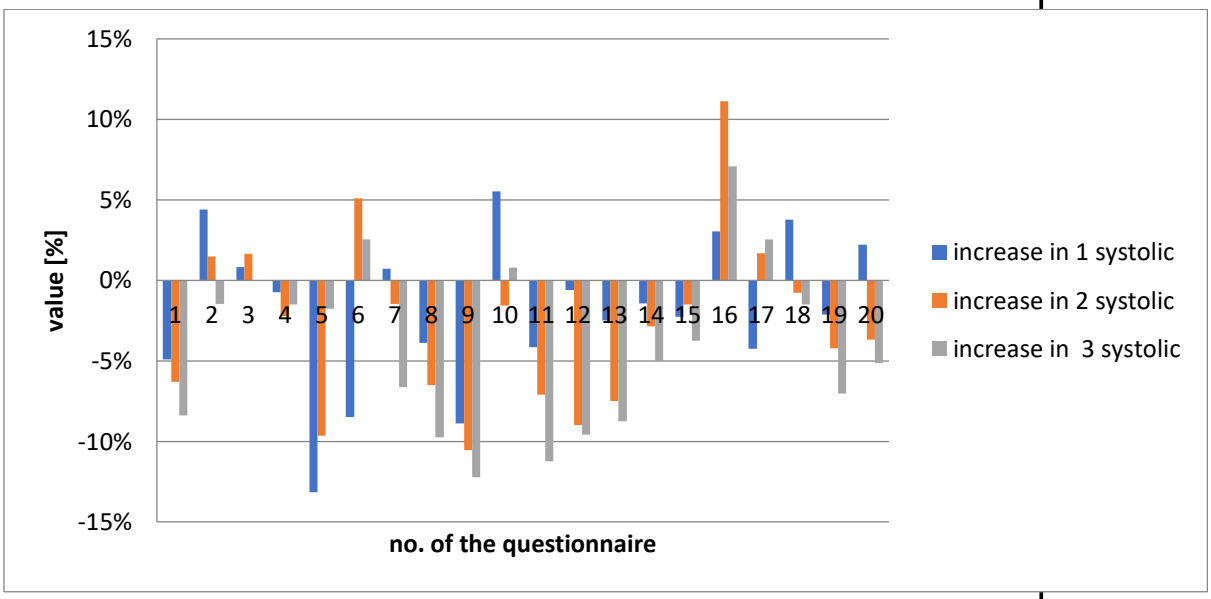


Figure 11. Graph of changes in the value of systolic blood pressure from the initial value in the study group

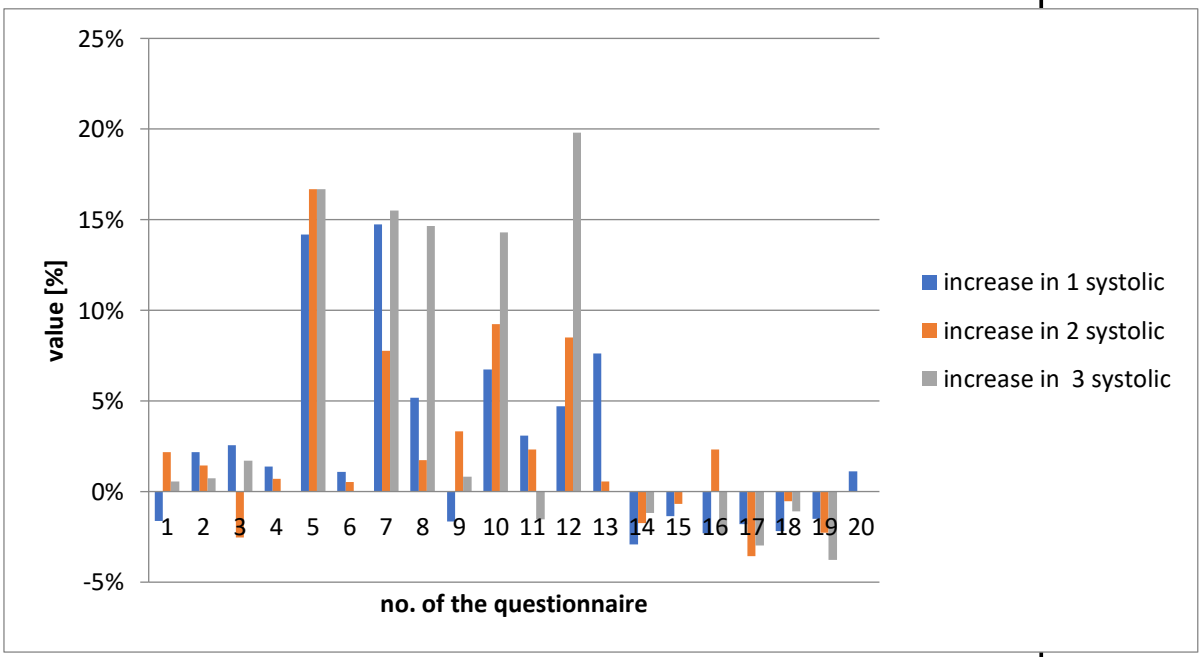


Figure 12. Graph of the decrease in systolic blood pressure from the initial value in the control group

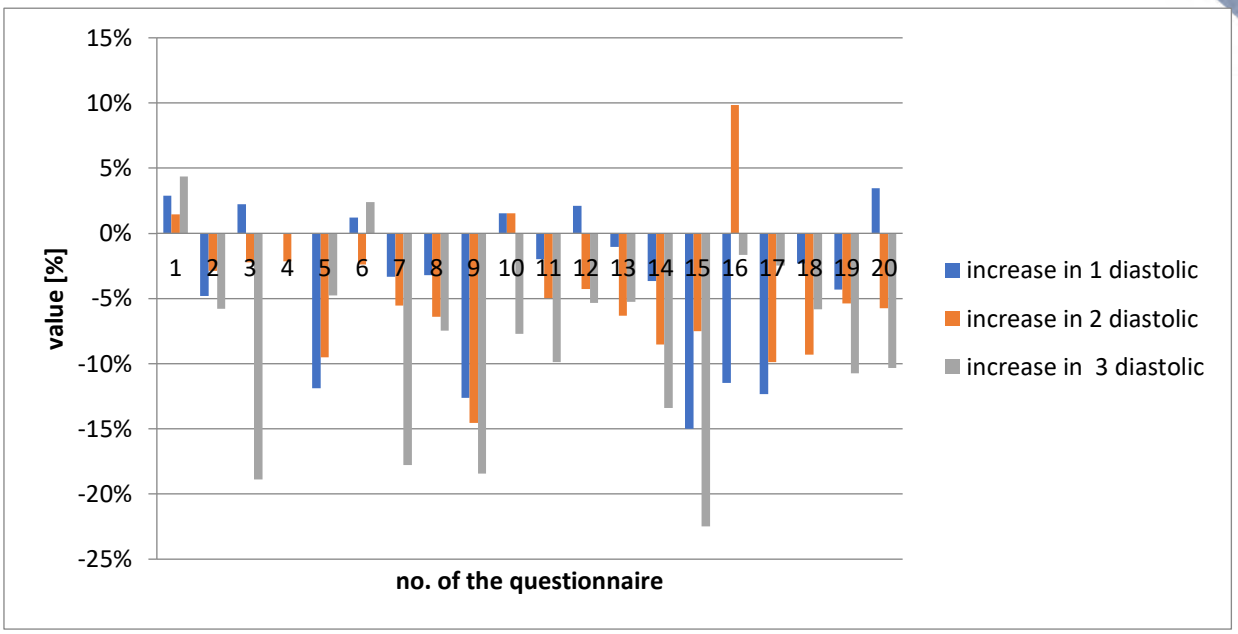


Figure 13. Graph of the decrease in diastolic blood pressure from the initial value in the study group

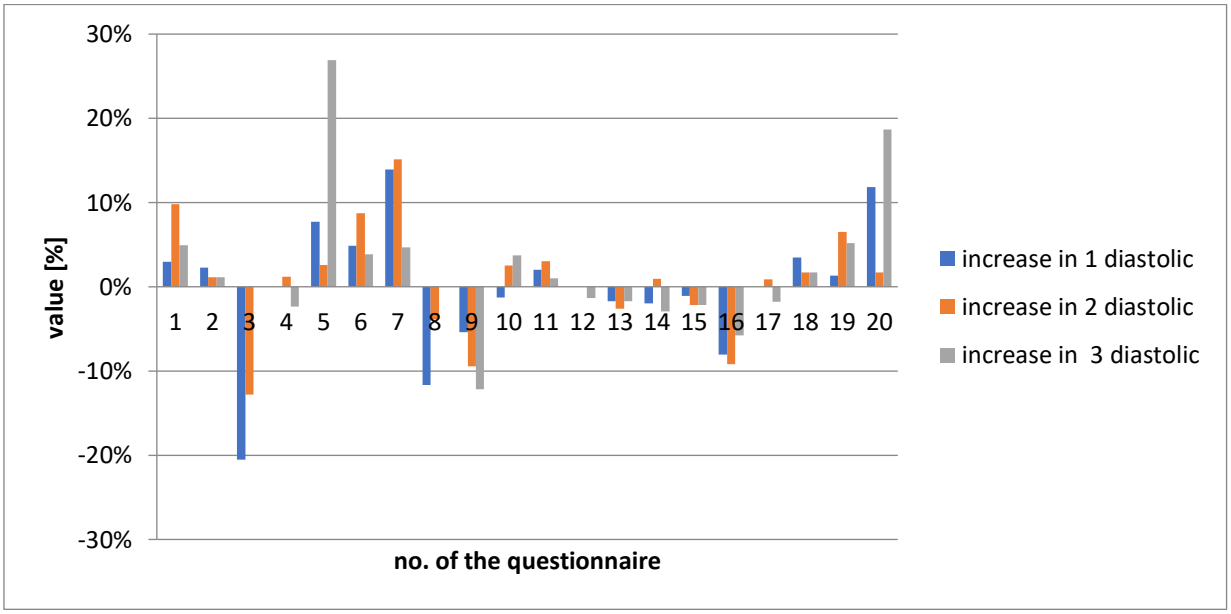


Figure 14. Graph of the decrease in diastolic blood pressure from the initial value in the control group

In the control group, the results were statistically significant (p <0,05): weight0: systolic0 -> 0.5800; mass1: systolic1 → 0.5696; mass2: systolic2 → 0.5362; mass3: systolic3 -> 0.5424.

- The situation was repeated during the analysis of the relationship between the diastolic blood pressure and the body weight. No statistical significance (p> 0.5) was found in the study group: systolic0 -> 0.2781; mass1: systolic1 → 0.2639; mass2: systolic2 →

0.2497; mass3: systolic3 -> 0.1000. In the control group, the results were statistically significant (p <0,05): weight0: systolic0 -> 0.6558; mass1: systolic1 → 0.6592; mass2: systolic2 -> 0.6044; mass3: systolic3 -> 0.6851.

- Interestingly, a statistically significant correlation at the level of p <0.05. Was established between the increase in systolic to diastolic blood pressure in both groups.

Table 5. Summary of the systolic and diastolic blood pressure of the entire population by quarterly division

	The marked correlation coefficients are significant at p < .0500			
Variable	DIASTOLIC 0	DIASTOLIC 1	DIASTOLIC 2	DIASTOLIC 3
SYSTOLIC 0	0.8292	0.7926	0.7934	0.7008
SYSTOLIC 1	0.8093	0.8142	0.8194	0.7359
SYSTOLIC 2	0.8189	0.8185	0.8457	0.7694
SYSTOLIC 3	0.7964	0.7972	0.8414	0.7838

The study population throughout the experiment had normal sodium (135-146 mg / dL) and potassium (2.5-5 mg/dL) levels. The dependence of the change in heart rate on the value of systolic and diastolic pressure was compared. In the study group, a correlation was obtained between the values of systolic blood pressure and pulse at the significance level of p <0.05, while a statistically significant correlation of both systolic and diastolic pressure about the pulse value was obtained in the control group. In the experimental group, the blood pressure and heart rate values were regulated. The systolic blood pressure decreased directly to the pulse rate, and the diastolic blood pressure decreased irrespectively of the systolic blood pressure and HR. On the other hand, the increase in the systolic and diastolic pressure increased proportionally in the control group, as did the pulse value. The correlation was in the range of 0.56-0.78.

During the nine months, no statistically significant change in the TG level was observed in the study and control groups (p> 0.05). In both groups, the value of triglycerides has a statistically significant and directly proportional (correlation 0.6) effect on the systolic blood pressure level and the total cholesterol level. In the experimental group, the values decreased, while in the control group, they increased. In the experimental group, correlations between the values of LDL and total cholesterol were observed. There was no correlation between HDL and total cholesterol. In the control group, the value of LDL increased proportionally and statistically significantly with the total cholesterol level with a simultaneous decrease in HDL (the value was not statistically significant). The data obtained are presented below (Tables 6 and 7).

Table 6. Correlation of LDL and HDL with respect to total cholesterol in the experimental group

Variable	The marked cefficients of correlation are significant at p < .0500			
	CHOLESTEROL 0	CHOLESTEROL 1	CHOLESTEROL 2	CHOLESTEROL 3
LDL 0	0.6252	0.5843	0.5543	0.4813
LDL 1	0.5776	0.5848	0.5646	0.5008
LDL 2	0.4978	0.5172	0.5228	0.4646
LDL 3	0.4875	0.5211	0.5428	0.5086
HDL 0	0.0052	0.0659	0.1025	0.0961
HDL 1	0.0169	0.0814	0.1126	0.0971
HDL 2	0.0154	0.0687	0.1060	0.1092
HDL 3	0.0174	0.0621	0.0989	0.1219

Table 7. Correlation of LDL and HDL in relation to total cholesterol in the control group

Variable	The marked cefficients of correlation are significant at p < ,0500			
	CHOLESTEROL 0	CHOLESTEROL 1	CHOLESTEROL 2	CHOLESTEROL 3
LDL 0	0.9802	0.9838	0.9766	0.9466
LDL 1	0.9377	0.9599	0.9594	0.9449
LDL 2	0.9071	0.9407	0.9536	0.9570
LDL 3	0.8338	0.8855	0.9145	0.9480
HDL 0	-0.3717	-0.3635	-0.3706	-0.3847
HDL 1	-0.3831	-0.3795	-0.3863	-0.4017
HDL 2	-0.2838	-0.2869	-0.2969	-0.3235
HDL 3	-0.3045	-0.3128	-0.3272	-0.3581

In the experimental and control groups, no statistically significant (p> 0.05) correlation was found between the values of LDL and TG, and LDL and glycemia, although in the experimental group, the values of LDL, glycemia and TG decreased and increased in the control group. Markedly, proportionality was maintained in the increase in LDL level, decrease in HDL, and the increase in the body weight in the control group, in contrast to the experimental group. No correlation was found at the level of statistical significance of the above variables. Table 7 below presents statistically significant data obtained in the control group.

Table 8. Correlation of body weight and LDL level in the control group

Variable	The marked cefficients of correlation are significant at p < ,0500							
	LDL 0	LDL 1	LDL 2	LDL 3	HDL 0	HDL 1	HDL 2	HDL3
Weight 0	0.4998	0.5016	0.4928	0.4612	-0.5102	-0.5255	-0.5311	-0.5396
Weight 1	0.4694	0.4841	0.4777	0.4497	-0.5197	-0.5459	-0.5551	-0.5562
Weight 2	0.4431	0.4654	0.4642	0.4433	-0.5084	-0.5392	-0.5556	-0.5619
Weight 3	0.4298	0.4610	0.4701	0.4689	-0.5170	-0.5470	-0.5680	-0.5771

At the end of the experiment, the proprietary patient satisfaction questionnaire was conducted, which showed that all people in the experimental group felt a significant

improvement in their well-being and health condition. However, they were unsure if they would maintain their new life habits, as 60% of family members showed no willingness to support the change. In addition, the control group described their condition as average in 75%, 15 people - as worse, and two people - that they did not notice any changes.

Discussion

In 1974, the Canadian health minister introduced health dependencies in the form of "health fields." Health condition is determined mainly by lifestyle (50%), physical and social environment (20%), genetic factors (20%), and health care (10%) [21].

Lifestyle includes physical activity, diet, and exposure to stressors. In analyzing the factors of stroke, they all influence its development. It is also observed that a high body mass index (BMI) may increase the risk of ischemic stroke [9]. Another parameter is the ratio of the length of the hip belt to abdominal obesity (but not with BMI) or has no relationship [22-23]. As a result, being overweight is not included in the prognosis of stroke risk, nor is it listed as a significant risk factor for stroke by the National Institutes of Health or the American Stroke Association [24,25]. However, obesity is listed as a key modifiable risk factor for stroke in the American Heart Association guidelines [26].

It is emphasized in the literature that during controlled physical exercise, the tendency to aggregate blood cells decreases, HDL increases. In contrast, LDL decreases, which results in a 27% decrease in the risk of stroke and death [19]. The study group showed a significant decrease in weight, increased HDL levels, and decreased LDL. However, there was no correlation between weight loss and the decreased LDL levels. In contrast, in the control group, in which a correlation between the increase in the level of "bad" cholesterol and the increase in the body weight was shown.

Interestingly, a slight change was determined in the value of TG in the study and control group. The professional literature emphasizes that TG should decrease together with a decrease in LDL and an increase in HDL [13]. In our research, because no abnormalities were observed in the INR before the experiment, the impact of a stroke prevention program on the level of blood coagulation could not be assessed.

By performing aerobic exercise for 30 minutes 3-5 times a week, patients at risk of CVD reduce the likelihood of suffering a stroke by 15% [27]. In addition, the study participants had two of the following diseases: hypertension, diabetes, and atherosclerosis. The stroke

prevention program consisted in participating twice a week in 60-minute aqua fitness classes conducted by a qualified instructor. In the professional literature, this form of training is significantly better than exercise, for example, in the gym [28]. The most important advantages of the above include teamwork, cooling the body during exercise, and the work of many muscle groups de-stresses and improves the functioning of the circulatory and respiratory systems. Moreover, Kinet confirms that exercise in the water – aqua aerobic improves physical fitness and reduces CVD risk [18].

One of the most beneficial diets for vascular diseases is a vegan or Mediterranean diet. Switching from saturated fatty acids to EFAs or complex carbohydrates reduces the relative risk of stroke by 25% [29,30]. It is recommended to consume about 30 grams a day of walnuts, hazelnuts, or almonds, but in a natural form, without adding spices [16].

The level of glycemia also has a significant impact on the development of stroke. As a result of glycogenogenesis, sugars are transformed into fat particles, consequently increasing the level of lipids [31]. Carbonated drinks are sweetened and significantly affect blood sugar levels, so it is recommended to replenish/supplement liquids with mineral water with low sodium content. In the present study, a clinical dietitian created a diet that the experimental group introduced. It contained five balanced meals, which consisted of products chosen by people from the study group as the ones they like and use in everyday life. For the dietitian's copyright reasons, it has not been described in this article. However, it was based on the guidelines mentioned above.

The data obtained confirm that diet and physical activity significantly affect the level of blood pressure. The above was also confirmed by Nagashima [32]. Interestingly, in the study group, there was a correlation between the decrease in the heart rate and the decrease in the systolic blood pressure, but there was no correlation between HR and DBP. On the other hand, there was a correlation between the increase in the parameters such as heart rate and systolic and diastolic blood pressure in the control group. The literature data suggest that blood pressure should increase with increasing heart rate [33]. The results in the control group also confirmed the above results. Pilis et al. [34] observed that physical activity and a rational diet positively influenced glycaemia. The data obtained from the studies conducted show that glycemia is normalized among women in the study group. However, no correlation was found between the glycaemia value and LDL, HDL, and TG in the control and experimental groups. The literature confirms that LDL levels decrease and HLD levels increase due to weight loss, with the simultaneous normalization of blood sugar levels [35-36]. In the present study, it was found

that the blood glucose level was normalized in the group that actively participated in the stroke prevention program after the experiment.

The emotional state affects the entire body. Stress, aggression, disapproval, and rejection are potent stimuli that affect the behavioral and hemodynamic zones. Negative emotions cause the vascular endothelium to form atherosclerotic plaque on its surface. On the other hand, secondary hypertension is caused by the release of catecholamines and cortisol and stimulated macrophages to intensify the inflammatory process and increase blood cells' aggregation [37,38].

The examples listed confirm the definition of health provided by WHO, i.e., "health is not only the complete absence of disease or disability but also the state of complete physical, mental and social well-being" [4,39]. Furthermore, this definition explains that the focus should be on enhancing health through prophylaxis (disease prevention) and not solely on treatment.

Summing up, the prevention of stroke has a significant benefit for people at risk of the disease, to prevent its occurrence (primary prevention), and for people who have had an episode of stroke (secondary prevention). The current state of knowledge indicates the significant and constantly growing importance of non-pharmacological activities undertaken as part of primary prevention of stroke, which is complementary to pharmacological therapy and an equally important area of intervention. The first one is mainly related to the minimization of risk factors. Methods of non-pharmacological prevention include, on the one hand, appropriate targeting and the introduction of the patient's regular activity. On the other hand, the need for early and common education on the purpose, scope, and benefits of introducing the broadly understood principles of a healthy lifestyle. In secondary prophylaxis and pharmacological treatment, a broadly understood lifestyle modification is essential, which helps to control better individual risk factors. It should also be remembered that an effective form of lowering diseases involves support from the family and loved ones. They motivate each other to control their lives.

References

1. Boehme A.K., Esenwa C., Elkind M.S.: Stroke risk factors, genetics, and prevention Circulation Research, 2017, 120(3), 472-495.
2. Litwin T., Członkowska A.: Udar mózgu -wprowadzenie.-Brain stroke- introduction [in:] Neurologia, Warszawa. Medical Tribune Polska, Tom II, 2014, 171-180.
3. Litwin. A., Członkowska A. Niedokrwienny udar mózgu. Jak zapobiegać i leczyć. Czyniki Ryzyka - Ischemic stroke. How to prevent and treat. Risk Factors, 2013, 2,19-32.

4. Donkor E.S.. Stroke in the 21(st) Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. Stroke Research And Treatment, 2018, 27, 3238165.
5. Ratajczak B., Kwapisz U.: Metody prewencji w odniesieniu do pacjent ow niepełnosprawnych po przebytym udarze mózgowym. Pielęgniarstwo Polskie - Prevention methods in relation to patients with disabilities after cerebral stroke. Polish Nursing, 2008, 4(30), 277-282.
6. Ovbiagele B., Nguyen-Huynh M.: Stroke epidemiology: advancing our understanding of disease mechanism and therapy. Neurotherapeutics, 2018, 8, 319–329.
7. Krajnik-Gwóźdź A., Kmieć T.: Udar mózgu u dzieci i młodziezy. Klinika Pediatryczna - Stroke in children and adolescents. Pediatric Clinic, 2006, 14(4), 460-465.
8. O'Donnell M.J., Denis X., Liu L.: Interstroke Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. The Lancet, 2010, 376(9735), 112–123.
9. Kurth T., Gaziano JM., Berger K., Kase C.S., Rexrode K.K., Cook N.R., Buring J.E., Manson J.E.: Body Mass Index and the Risk of Stroke in Men. Polish Archives of Internal Medicine, 2002, 162, 2557-2562.
10. Czech A., Łaz R., Robiec A.: Cukrzyca a udar niedokrwienny mózgu - Diabetes and ischemic stroke. Medycyna Metaboliczna, 1998, 2(2), 48-54.
11. Baczyńska A.: Doustne leki przeciwkrzepliwe w różnych stanach klinicznych. Choroby serca i naczyń - Oral anticoagulants in various clinical conditions. Heart and vascular diseases, 2004, 1(1), 27-36.
12. Wolski H.: Wybrane aspekty działań niepożądanych złożonej doustnej antykoncepcji hormonalnej. Ginekologia Polska - Selected aspects of side effects of COCs. Polish gynecology, 2014, 12, 944-949.
13. Użarowska M., Surman M., Janik M.: Dwie twarze cholesterolu: znaczenie fizjologiczne i udział w patogenezie wybranych schorzeń. Kosmos. Problemy Nauk Biologicznych - Two faces of cholesterol: physiological importance and participation in the pathogenesis of selected diseases. Cosmos. Problems of Biological Sciences, 2018, 6/7(2), 375-390.
14. Kosmas C.E., Martinez I., Sourlas A., Bouza K.V., Campos F.N., Montan P.D., Gurzman E.: High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease. Drugs Context, 2018, 7, 212525.
15. Szymański F.M., Barylski M., Cybulska B. et al.: Rekomendacje dotyczące leczenia dyslipidemii w Polsce -III Deklaracja Sopocka Interdyscyplinarne stanowisko grupy

ekspertów wsparte przez Sekcje Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego. Choroby Serca i Naczyń, - Recommendations for the treatment of dyslipidemia in Poland - 3rd Sopot Declaration Interdisciplinary position of an expert group supported by the Sections of Cardiovascular Pharmacotherapy of the Polish Society of Cardiology. Heart and Vascular Diseases, 2018, 15(4), 199-210.

16. Jankowski P.: Zasady Profilaktyki chorób układu krążenia w 2018 roku. Kardiologia Inwazyjna - Rules for the prevention of cardiovascular diseases in 2018. Invasive cardiology, 2017, 5(12), 42-48.
17. Budzyński J., Wiśniewska B.: Statyny w pierwotnej i wtórnej prewencji udaru niedokrwiennego mózgu. Forum Medycyny Rodzinnej - Statins in the primary and secondary prevention of ischemic stroke. Family Medicine Forum, 2014, 8(1), 1-8.
18. Kasprzak Z., Pilaczyńska-Szcześniak Ł.: Effects of regular physical exercises in the water on the metabolic profile of women with abdominal obesity. The Journal of Human Kinetics, 2014, 41, 71-79.
19. Chong J., Sacco R. Risk factors for stroke, assessing risk, and the mass and high-risk approaches for stroke prevention. [In:] Gorelick PB, ed. Continuum: Stroke Prevention. Hagerstwon, Maryland: Lippincott Williams and Wilkins, 2005, 18–34.
20. Lee J.S., Chang P.Y., Zhang Y., Kizer J.R., Best L.G., Howard B.V.: Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: the strong heart study. Diabetes Care, 2017, 40(4), 529- 537.
21. Strożyńska E., Ryglewicz D.: Czynniki udaru mózgu u kobiet. Polski Przegląd Neurologiczny - Stroke factors in women. Polish Neurological Review, 2013, 9(4), 135-139.
22. Walkers S.P., Rimm E.B., Kawachi I., Stampfer M.J., Willett W.C.: Body size and fat distribution as predictors of stroke among USmen. American Journal of Epidemiology,1996, 144. 1143-1150.
23. Curb J.D., Marcus E.B.: Body fat coronary heart disease, and stroke in Japanese men.am. The American journal of clinical nutrition, 1991, 53, 1612-1615.
24. National Institute of Neurological Disorders and Stroke. Stroke risk factors and symptoms. Available at: http://www.ninds.nih.gov/health_and_medical/pubs/stroke_bookmark.html. (cited 19.08.2021).
25. American Stroke Association. Stroke risk factors. Avaliable at: http://www.strokeassociation.org/presenter.jhtml?identifier=1060. (cited 19.08.2021).
26. GoldsteinL.B. , Adams R., Becker CD, Gorelick PB, Hademenos G., Hill M., Howard G.,

Howard VJ, Jacobs B., Levine SR, Mosca L, Sacco RI, Sherman DG, Wolf PA, Del Zoppo GJ. Primary prevention of ischemic stroke: a statement for healthcare professionals from the stroke council of the American Heart Association. Stroke, 2001, 32, 280-299.

27. Antecki. J., Brylak E., Sobolewski P., Kozera G.: Profilaktyka pierwotna i wtórna udaru niedokrwiennego mózgu w świetle obecnych zaleceń i rekomendacji. Forum Medycyny Rodzinnej - Primary and secondary prevention of ischemic stroke in the light of current recommendations and recommendations. Family Medicine Forum, 2018, 12, 3, 89-98.
28. Hossein Abdadi et al. l: Effects of aqua-aerobic exercise on the cardiovascular fitness and weight loss among obese students. Int. J. Physiother., 2017, 4(5), 279-282.
29. Hu F.B., Willett W.C.: Optimal diets for prevention of coronary heart disease**.** JAMA, 2002, 288, 2569–2578.
30. Śliz D., Zgliczyński W.S., Szeligowska J. et all: Modyfikacja zwyczajów żywieniowych w prewencji chorób cywilizacyjnych - Modification of eating habits in the prevention of civilization diseases. Post. N. Med., XXIX, 2016, 5, 344-349.
31. Otto-Buczkowska E.: Hipoglikemia chorych z cukrzycą. Forum Medycyny Rodzinnej - Hypoglycemia in diabetic patients. Family Medicine Forum, 2017, 11, 6, 237-242.
32. Nagashima J. et al. l: Three-month exercise and weight loss program improve heart rate recovery in observed persons along with cardiopulmonary function. Journal of Cardiology. July 2010, 56(1), 79-84.
33. Schoenenberger A.W. et al. l: Effects of weight on blood pressure at rest and during exercise. Hypertension Research, 2013, 36, 1045-1050.
34. Wpływ rodzaju stosowanej diety i aktywności ruchowej na masę ciała i funkcjonowanie organizmu - Influence of the type of diet and physical activity on the body weight and functioning of the body: http://agro.icm.edu.pl/agro/element/bwmeta1.element.agro-45f17242-4400-48af-8388-a7b2cb24569b/c/133-150.pdf. (cited 19.08.2021).
35. Yaates T. et al.: The role of physical activity in the management of impaired glucose tolerance: a systemic review. Diabetologia, 2007, 50, 1116-1126.
36. Colbers S.R. et al.: Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care, 2016, 39, 2065-2079.
37. Jonas B.S., Mussolino M.E.: Symptoms of depression as a prospective risk factor for stroke. Psychosom Med., 2000, 62, 463-471.
38. Guzik. P.: Wpływ stresu na układ krążenia. Forum Kardiologów - The influence of stress on the circulatory system. Cardiologists Forum, 2001, 6, 2, 53-57.

39. Kanteluk A.A., Krajewska-Kułak E., Fiłon J.: Wykorzystanie wybranych zasad ergonomii w życiu codziennym w percepcji studentów pielęgniarstwa i chemii–doniesienie wstępne - The use of selected principles of ergonomics in everyday life in the perception of nursing and chemistry students - introductory report . Problemy Higieny i Epidemioloogii, 2005, 96, 1, 269-278.

CHALLENGES RELATED TO THE SARS-CoV-2 EPIDEMIC

Addictions and habits during COVID-19 Pandemic - their impact on healthcare system

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Introduction

It has already been over a year since the beginning of the Pandemic caused by the SARS-COV-2 virus, which causes COVID-19 disease. During this time, life around the world has changed so radically; nobody could expect such change at all. A significant part of the business moved to the cloud network - people are working more and buy more frequently online. Similarly, it happened also in education. As a result of the closure of schools and universities, students remained at homes, at their desks, learning remotely.

Social changes that are currently happening have become a subject of interest in various scientificenvironments. There is innumerable research in many areas - economics, psychology, medicine. One of the often-undertaken topics is the problem of addictions in the face of the prevailing Pandemic.

How do people deal with these at an additional burden that a virus and Pandemic is causing?

Is the number of addicted people increasing or decreasing?

Are the existing problems deepening?

More and more publications on people's general health during the Pandemic and how it changes due to slowdown caused by a threat resulting from a virus, closing peopleat home and

reducing social contacts to a minimum.

We will not get a thorough answer to such questions just yet. For now, we can try to find the overall direction of changes and problems that may result from the Pandemic. In the presented work, we focused on the description of the discussed phenomena and analysis of the survey conducted among students of medical universities – which allowed us to indicate that the problems also apply to people associated with health protection. It is necessary for society and its leaders to be aware of brewing issues – they can turn into an unpleasant surprise if we do not deal with them efficiently. These problems affect all of us.

Alcohol

Alcohol hurts the functioning of the immune system on many planes. Inthis topic, its excessive consumption must make it easy for respiratory diseases, including pneumonia, tuberculosis, or acute respiratory failure, todevelop [1]. We must not forget that this group of diseases also includes COVID-19.

Alcohol abuse 'works well' with loneliness, the requirement to maintain social distance, and even a false belief on the effectiveness of alcohol as a cure for the disease. For example, the aftermathof belief described above was that some thought alcohol consumption could protect against coronavirus infection. However, drinking alcohol does not destroy the virus and hurts the immune system. Instead, it uses high-percent alcohol - at a concentration of a minimum of 60% - which can be used to disinfect the surface [1].

The first study on alcohol consumption during the SARS-COV-2 Pandemic was carried out in April 2020 and covered several hundred Poles [2]. The respondents were assessedbased on recognized tests, including the Audit test developed by the WHO (Screen Testdetecting alcohol problems), PSS 10 questionnaire (assessing the level of stress), or a Mini- Cope questionnaire (assessing strategies to deal with stress). It turned out that almost 30% of respondents changed their habits - 16% drank less alcohol, and 14% consumed more compared to the pre-Covid-19 period. On the other hand, nearly 30% of respondents consumed alcohol in excessive amounts, which significantly exceeds the current percentage of this phenomenon in our country.

The increase in alcohol consumption in response to crises is a well-known phenomenon. They were observed both after the passage of Hurricane Katrina or after attackson the World Trade Center and during the economic crisis in 2007-2009. Epidemic also includes this trend,

which indicates a significant increase in alcohol consumption in Asia countries during the SARS epidemic of 2003 [3].

What are the causes of this behavior? It turns out that people who enjoy larger amounts of alcohol during the Pandemic have already been drinking excessively. Significantly, these people rarely or never developed positive strategies to deal with stress, reaching for various stimulants instead. Conclusion This has a direct relationship between mental disorders development, which has a base of an anxiety caused by fear of infection, lockdown, a sense of loneliness during isolation, and fear of financial problems. However, the intensity of changes in the psyche during the Pandemic is different - from disorders of concentration and insomnia to anxiety or depression disorders. The results of research conducted in GreatBritain, the USA, and Greece are also alarming, which showed that during Covid-19 Pandemic the suicides increased by as much as 60% [3].

Smoking

The uncontrollable Pandemic and unpredictability related to COVID-19 led to tangible health, social and economic consequences. Life in uncertain times and the loss of existing life stability directly translate into increased stress. A combination of prolonged anxiety, limitations of living space, and social isolation causes an increase in interest in various types of stimulants, including tobacco products, as a way of coping with constant stress caused by apandemic [4].

It has been shown that smoking is associated with a worse Covid-19 response. For smokers, there is a more frequent need for hospitalization, and the risk that the condition of such people in the course of the disease will be heavy or critical is twice as high as in people whohave never smoked [5]. Therefore, it would seem that understanding the consequences of smoking cigarettes in the era of Covid-19 could serve as an excellent motivation to stop smoking. On the other hand, prolonged stress does not promote breaking with addiction and even causes areturn to addiction among people who have already managed to stop.

Despite the relatively short duration of the Pandemic, several research on the influence of COVID-19 on habits related to cigarettes and smoking have already been carried out. For example, in Poland, 45.2% of smokers began to smoke more, 40.0% did not notice any change, and 14.8% were not sure if a change in their habits occurred [6].

According to the Belgian team under the leadership of N. Vanderbruggen, analysis based

on 3632 subjects revealed that15.4% were smokers before the burst of the Pandemic. 1% of the entire group of respondents ceased smoking, and 0.9% of the same group started smoking, even though they had never smoked before. 7.4% of the respondents began to smoke more; for comparison, 2.5%, admitted that during the Pandemic, they smoked less. An age, a kind of work, and education remained relevant in the test study. It has been shown that younger people smoked more. When people with higher education were accepted as a reference group, the studies showed that people holding a doctorate were 76% less inclined to reach for cigarettes, while people with lower education smoked much more frequently. The most significant tendency tothe increased smoking was with people with vocational education. The chance of starting smoking / increasing their habit was more than twice as high as in the reference group [7].

J. Bombele et al. conducted a study among Danish smokers and showed that more respondents increased smoking (18.9%) than the reduced (14.1%) in connection with the Covid-19 Pandemic. For these two groups, motivations were extremely different. Among those limiting smoking, the main reasons for reducing the addiction were the desire to be healthier (32.3%), more time being spent in loneliness (27.7%), the desire to have healthier lungs (20.7%). As an argument for an increase in smoking, the answers smokers gave the most frequently were boredom (48.6%), increased perception of stress (43.2%), and more time spent in loneliness (36.6%) [8].

These arguments largely coincide with research carried out in Belgium. In contrast, three main reasons for increased cigarette smoking were boredom, no contact with others, and the loss of the existing structure of the day [6].

In the current situation, it cannot be determined whether the Covid-19 Pandemic had a significant impact on cessation or increase of smoking. It became more difficult for many to break with addictions due to the world-prevailing conditions associated with employment uncertainty, stress, difficulty mobility, or boredom. On the other hand, some feel more motivated to break with addiction, and in some, pandemics evokes a demotivating effect [6,8].

Internet

Among addictions, we can distinguish behavioral addictions, i.e., addiction to performing certain activities that may be a source of pleasure or bring relief to internal suffering [9]. The development of technology has undoubtedly brought with it many amenities

in almost every aspect of life and contributed to the emergence of new types of addiction - to the Internetand its dependencies on social media or online gaming.

The Internet is a particularly attractive tool for young people to communicate with others, share events from their lives and gain knowledge. Although there is no clear definition of Internet addiction, there is a loss of control over Internet use, contributing to neurological and psychological disorders and impoverishing socialization in everydaylife [10]. It has been shown that excessive use of the Internet is often associated with poor health, not only physically but also mentally, and is utilized to cope with difficulties and stress in everyday life [11,12].

It should be emphasized again that the outbreak of the COVID-19 Pandemic led to a reduction in social contacts, an increase in the feeling of anxiety and stress [13]. A study conducted among students by Lithuanian scientists showed that as many as 76% of respondents indicated at least a moderate increase in the time they spend on Internet activity. Of the students, 45.1% reported being addicted to the Internet, 38.1% reported feelinganxious, and 43.6% had moderate to severe depressive symptoms. It was noticed that anxiety and depressive symptoms appeared significantly more often among people who excessively use the Internet [14].

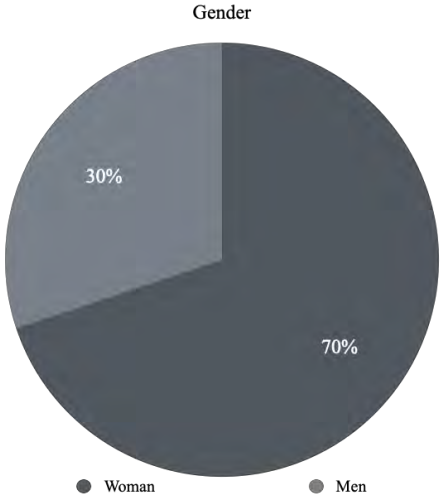
Another study compared the prevalence of internet addiction during the COVID-19 Pandemicamong Egyptian medical and non-medical students. It found that 51.7% of medical students were found to be heavily addicted to the Internet, and 43.3% of them were likely to be addicted. For comparison, 11.3% of students of non-medical faculties were considered severely addicted, and 68.9% were probably addicted [15].

Survey Analysis

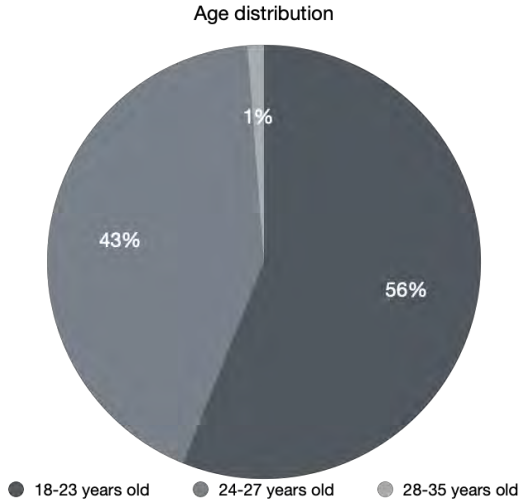
Using an internet form, an anonymous questionnaire was carried out among 83 students of medical universities. A group of respondents consisted of 58 women and 25 men (Graph 1).

Age distribution was presented in chart No. 2 - 56% of people belonging to the group were younger than the 23rd year of age, 43% were within limits between 24 and 27 years of age, and 1% were older (Graph 2).

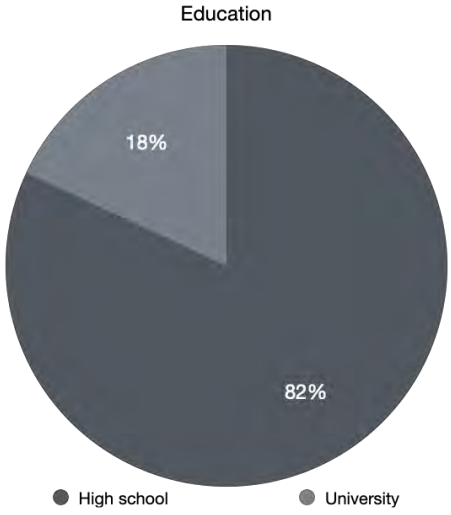
In addition, 18% of the respondents have already obtained higher education (Graph 3). Nearly 80% of people were medical students (Graph 4).



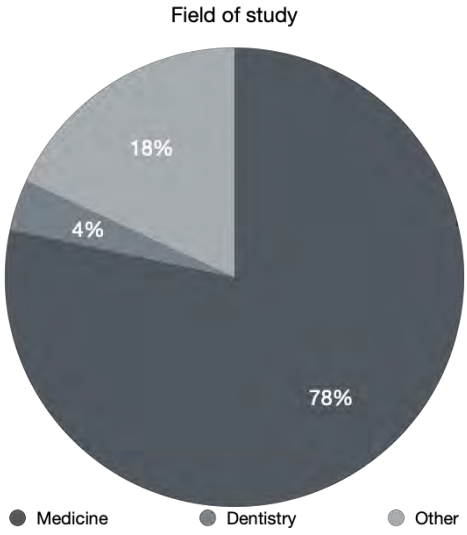
Graph 1



Graph 2

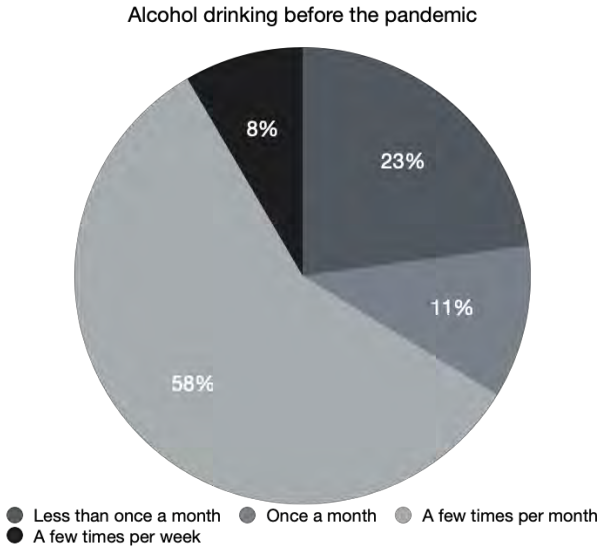


Graph 3

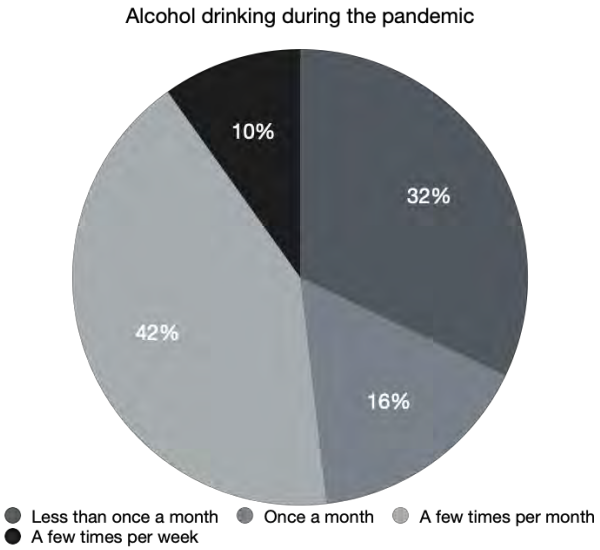


Graph 4

One of the topics discussed in the survey was the intake of alcoholic beverages by the respondents. Before the explosion of Pandemic SARS-COV-2, 32% of the respondents consumed alcoholic beverages less frequently than once a month, 16% consumed alcohol once a month, 42% several times a month, and 10% set them several times a week. The frequency has changed along with the explosion of a pandemic - the number of survey respondents which consumed alcohol less frequently than at a time of month dropped to 23%,once a month to 11% and several times a week to 8%. On the other hand, Pandemic significantly increased the number of people who consume alcohol several times a month - from 42% to 58% (Graph 5, Graph 6).



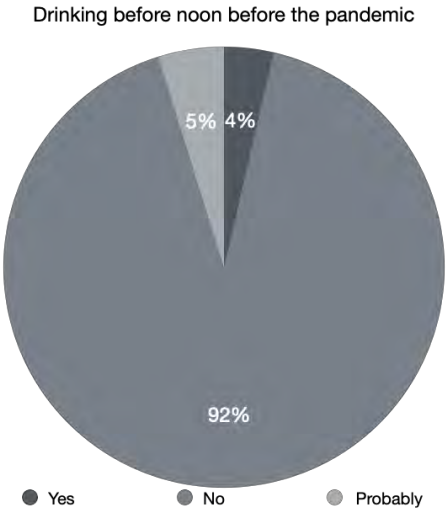
Graph 5



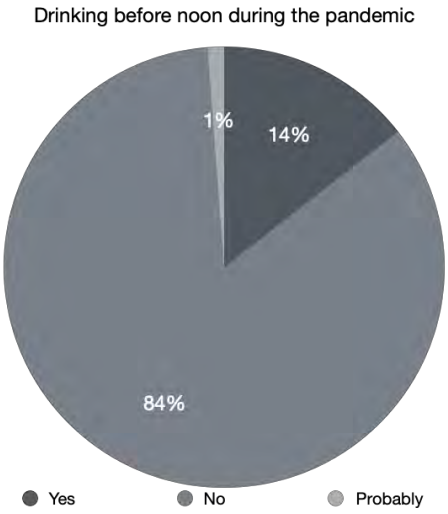
Graph 6

Interestingly, 6% of respondents have reduced the variety of alcoholic beverages consumed, while 20% have increased kind and drink types. The presented data is consistent with other analyzes - unfortunately, with the increasing duration of the Pandemic the amount of alcohol consumed by people has also increased. Undoubtedly, we will have to pay for this as a society by a future increase of detrimental health effects.

The custom of drinking has been reviewed. Before the Pandemic, 92% of the respondents answered 'no' when asked if consumption of alcoholic beverages commenced before noon. However, 4% openly admitted to drinking from the early morning. From March 2020, habits have changed - currently, only 84% of people strongly deny similar practices, 14% simply admit to them (Graph 7, Graph 8).



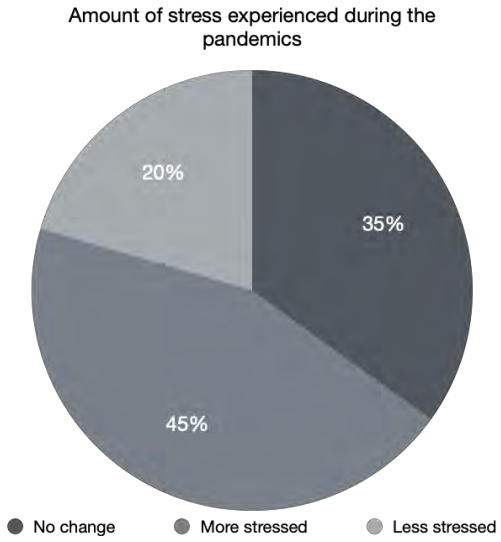
Graph 7



Graph 8

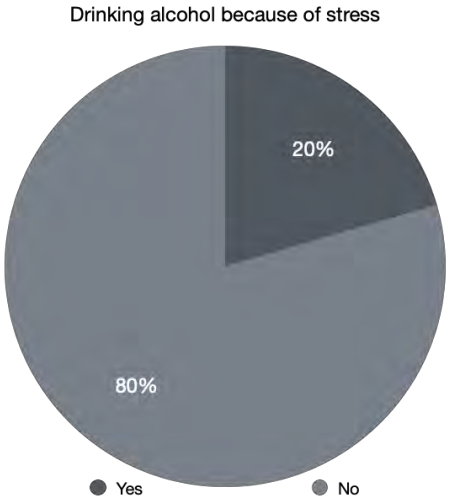
At the same time, as many as 12% of the respondents indicate that they have an alcoholic drink during classes or remote work. The likely cause may be a sense of isolation and closure, but it is not easy to review it more closely. Is it a general increase in the amount of alcohol consumed and subsequently the intensity of problems generated by it, or maybe people previously constrained by the social framework have lost this barrier? For example, a co-worker cannot smell the alcohol in the breath if all the work is doneremotely.

In 35% of the respondents, the amount of stress has not changed with the advent of the Pandemic. On the other hand, 20% of respondents feel calmer than before, while 45% feel more stressed (Graph 9).



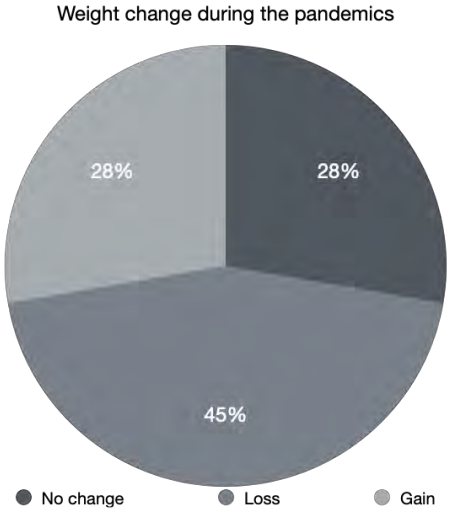
Graph 9

Some enjoy isolation – avoiding everyday contact with colleagues,they do not lose time to commute to classes or work and can relax or spend extra time with family. For others, reducing social contact is unfavorable and causes discomfort it is a significant group of people. 20% of people look to alleviate their mental tension in consuming alcoholic beverages (Graph 10).



Graph 10

Social isolation and confinement in homes allowed some to focus on personal development and implement beneficial behaviors into their lives, which could not be done previously due to lack of time and strength. As many as 54% of respondents claim that with the developmentof the Pandemic, they have developed a habit that is positive for their health. At the same time, 45% of them lost weight (Graph 11).



Graph 11

Summary

With the SARS-COV-2 virus pandemic, the number of identified negative health effects has increased, previously either poorly understood or insufficiently investigated.Such subjects are habits and addiction experienced by the people suddenly enclosed in their home, with limited contact with others.

One of the factors, which is probably the most dangerous in their long-term effects, isalcohol. As many studies showed, its consumption during the Pandemic increased. People reach for alcohol more likely, more often, earlier in the day. They use alcohol to relievestress; they stop responding to requirements of ongoing remote classes or urgent obligations. A continuous study of this topic is necessary - potential effects may significantly increasethe load of the healthcare systems that are already suffering from extra business caused by the pandemics. The phenomenon's scale is difficult to predict - from liver tumors, pancreas and esophagus, organ cirrhosis, to psychological and psychiatric problems. All these medicine fields will be meet with increasing demands. The faster the potential damage willbe estimated, the more efficiently it will be possible to prepare healthcare systems in individual countries.

The problem of addiction relates not only to chemical substances - a severe threat, especiallyin the present times, is a behavioral one with the Internet and accompanying phenomena, e.g.,social networks, mass media, or online shopping is an excellent example. Society closed in homes due to the prevailing Pandemic, spent a greater amount of time online. Thiscan lead to various addictions – spending a significant amount of time browsing countless messages on social networks and online shopping. The scale of the phenomenon is probably impossible to estimate - many of behaviors have been forced upon society due to isolation requirements, e.g., purchase of clothes without a visit to the store.

Psychologists' offices may crack in the seams in the future - the right branches of the health care system must be prepared for it.

Another threat is the reduction of physical activity. Society has been forced to close in homes within confines of limited space. People stopped to move - the daily number of steps and the floors taken has significantly decreased - many people were forced to work from home; similarly, schools began to function remotely.

The need for movement hasbeen reduced – with several stores moving into online space. In addition, gyms, swimming pools, and other sports centers have been closed for

a long time now. All ofthis resulted in a general limitation of moving among society. Lack of exercise is a known factor in developing all civilization diseases, from obesity to diabetes. In the survey, nearly one-third of the respondents took on weight.

In the future, healthcare systems worldwide will have to face the effects of the SARS-COV-2 virus pandemic. From the fight against civilization diseases and their complications to dealing with addiction and psychological and psychiatric problems. Potentially all branches of medicine stand in the face of a similar threat. Therefore, it is necessary to continuously explore the observed phenomena and preparing systems for the upcoming load – not yet defined and quite new – as is this pathogen.

References

1. Jaime A. Teixeira da Silva, Testino G.: Risks of alcohol abuse, alcoholism and stress-relateddrinking during the COVID-19 Pandemic. Alcohol Drug Addict 2020, 33(1), 95-98
2. Chodkiewicz J., Talarowska M., Miniszewska J., Nawrocka N., Biliński P.: Używanie alkoholu w dobie pandemii COVID-19 - badania polskie. Doniesienia wstępne. 2020, https://www.researchgate.net/publication/341459728_Uzywanie_alkoholu_w_dobie_pandemii_COVID_19_-_badania_polskie_Doniesienie_wstepne (data pobrania 20.07. 2021).
3. Capasso A., Jones A.M., Ali S.H., Foreman J., Tozan Y., DiClemente R.J.: Increased alcohol use during the COVID-19 Pandemic: The effect of mental health and age in a cross-sectionalsample of social media users in the U.S. Preventive Medicine, 2021, 145, 106422.
4. Zvolensky M.J., Garey L., Rogers A.H., Schmidt N.B., Vujanovic A.A., Storch E.A., Buckner J.D., Paulus D.J., Alfano C., Smits J., & O'Cleirigh C.: Psychological, addictive, and health behavior implications of the COVID-19 Pandemic. Behaviour Research and Therapy, 2020, 134, 103715.
5. Reddy R.K., Charles W.N., Sklavounos A., Dutt A., Seed P.T., Khajuria A.: The effect of smoking on COVID-19 severity: A systematic review and meta-analysis. Journal of Medical Virology, 2021, 93(2), 1045-1056.
6. Vanderbruggen N., Matthys F., Van Laere S., Zeeuws D., Santermans L., Van den AmeeleS., Crunelle C.L.: Self-reported alcohol, tobacco, and cannabis use during COVID-19 lockdown measures: Results from a web-based survey. European Addiction Research, 2020, 26, 309–315.

7. Sidor A., Rzymski P.: Dietary Choices and Habits during COVID-19 Lockdown: Experience from Poland. Nutrients, 2020, 12(6), 657.
8. Bommele J., Hopman P., Walters B.H., Geboers C., Croes E., Fong G. T., Quah A., & Willemsen, M.: The double-edged relationship between COVID-19 stress and smoking: Implications for smoking cessation. Tobacco induced diseases, 2020, 18, 63.
9. Lelonek-Kuleta B.: Uzależnienia behawioralne – podstawy teoretyczne. [W:] Uzależnienia behawioralne i zachowania problemowe młodzieży. Teoria-Diagnoza-Profilaktyka-Terapia. Jarczyńska J. (red.). Wydawnictwo Uniwersytetu Kazimierza Wielkiego, Bydgoszcz, 2014, 15-29.
10. Monacis L., Sinatra M., Griffiths M.D., de Palo V.: Assessment of the Italian version of the Internet Disorder Scale (IDS-15). The International Journal of Mental Health and Addiction, 2018, 16, 680-691.
11. Dong H., Yang F., Lu X., Hao W.: Internet Addiction and Related Psychological Factors Among Children and Adolescents in China During the Coronavirus Disease 2019 (COVID-19) Epidemic. Front Psychiatry, 2020, 11, 00751.
12. Liang L., Zhou D., Yuan C., Shao A., Bian Y.: Gender differences in the relationship between internet addiction and depression: a cross-lagged study in Chinese adolescents. Computers in Human Behavior, 2016, 63, 463-470.
13. Xiong J., Lipsitz O., Nasri F., Lui L.M.W., Gill H., Phan L., Chen-Li D., Iacobucci M., Ho R., Majeed A., McIntyre R.S.: Impact of COVID-19 Pandemic on mental health in the general population: A systematic review. Journal of Affective Disorders. 2020, 1(277), 55-64.
14. Gecaite-Stonciene J., Saudargiene A., Pranckeviciene A., Liaugaudaite V., Griskova-Bulanova I., Simkute D., Naginiene R., Dainauskas L.L., Ceidaite G., Burkauskas J.: Impulsivity Mediates Associations Between Problematic Internet Use, Anxiety, and Depressive Symptoms in Students: A Cross-Sectional COVID-19 Study. Frontiers in Psychiatry, 2021, 28(12), 634464.
15. Shehata W.M., Abdeldaim D.E.: Internet addiction among medical and non-medical students during COVID-19 Pandemic, Tanta University, Egypt. Environmental Science and Pollution Research, 2021, 20, 1–8.

Changes in sleeping behaviours and their consequences among home students duringSARS-CoV-2 pandemic

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Abbreviation list

- PIMS-TS- Multisystem Inflammatory Syndrome in Children temporally related to SARS-CoV -2
- ASS- acetylsalicylic acid
- ADHD- attention-deficit hyperactivity disorderCOVID-19- coronavirus disease 2019
- SARS-CoV-2- severe acute respiratory syndrome coronavirus 2

Introduction

More than a year after the start of the SARS-CoV-2 pandemic, it continues to significantly affect people's daily lives in most countries in the world.

In Poland, one of the most affected groups are students, who have been forced to study remotely for months. On May 11, 2020 all classes in Poland were suspended, initially for two weeks [1], but as a result, students did not return to school until the end of the school year (June 26) [2].

Theexceptions were the final 8th grade exams and the high school graduation exams, for which students had to physically appear at schools. In the following school year all students started in-person classes [3]. However, on October 24 2020 [4], due to the worsening epidemic situation, schools were closed again. The youngest students (I-III grades of primary

school) have returned to in-person schooling on May 4 2021, the rest of them- on May 29 2021 [5]. According to different studies, the sleeping behaviour during Covid-19 pandemic may change in a variety of ways [6–8]. In relation to home-office work, sleep disruption, changes in sleep schedule have been reported [6,8].

The effects of COVID-19 and linked with its homeschooling on children are a relatively unexplored area with limited information available on disease transmission, mortality, and theburden of symptomatic illnesses in children. Children nowadays have to struggle not onlywith new ways of learning but also existential fear. Very few cases were reported in the first few months of the pandemic. Confirmed cases in children, most of which were due to close contact with an infected family member. This landscape seems to have changed in the lastfew months. Up to 20% of confirmed cases were reported in young adults. That can play a rolein preventing community transmission. On the other hand, it is important to consider the impact of school closings and closings on the lives of young children. Alleviate the psychological distress associated with social distancing in young people.

We decided to check if sleeping behaviour has changed among Polish students from beforethe pandemic and how it manifests.

Aim

The study aims to compare the variety of changes in sleeping of students in Poland during homeschooling.

Materials and methods

The study included a group of 441 randomly selected school students who participated in remote classes. One hundred three of the respondents attend primary school, and 338 attend secondary school.

The research was conducted from May 1, 2021, to May 7, 2021, using a proprietary online questionnaire, created for this study. The questionnaire was publishedon Polish forums, groups and portals intended for school students. The questionnaire was anonymous and complied with the current provisions on the protection of personal data. All data obtained during the study were generalized and used in a collaborative study. The questionnaire

contained a total of 22 questions. The questions included in the questionnaire concerned: gender, place of residence, type of school and class, hours of falling asleep now and before the pandemic, number of naps now and before the pandemic and their length, amount of sleep now and before remote learning, and personal impressions of sleep, tirednessdaily and during remote lessons.

Excel version 16.48 was used for statistical analysis.

54,3% of the respondents were women, 43,9% were men, and the remaining 1.8% did not identify with any of the above genders.

The respondents participating in the study most often lived in small towns below 200,000. Inhabitants (36,5%), 33,5% of the respondents lived in the countryside, and the remaining 30% in large cities with more than 200,000 residents.

Results

328 of 441 (74,38%) surveyed responded that they had experienced a change in sleep qualitysince homeschooling began, including 192 (58,53%) women, 129 (39,33%) men and 7 (2,14%) persons that determine their sex as "other." Among them, 208 (47,17%) responders estimated that their quality of sleep has deteriorated, in contrast to the other 120 (27,21%) students, who indicated an improvement in sleep quality.

113 responders (25,62%) did not indicate any change in their sleep, including 43 (38,05%) women, 60 (53,10%) men and 10 (8,85%) persons that determine their sex as “other” (Fig.1).

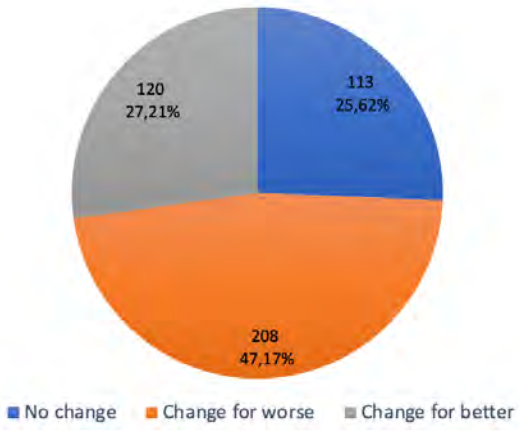


Figure 1. Change in the quality of sleep among students since the beginning of homeschooling

There is a statistical correlation between gender (male and female) and the occurrence ofsleep change (p=0,0105).

70,98%, that is, 313 of surveyed admitted that they do not feel well-rested during classes.29,02% (128) denied it (Fig. 2).

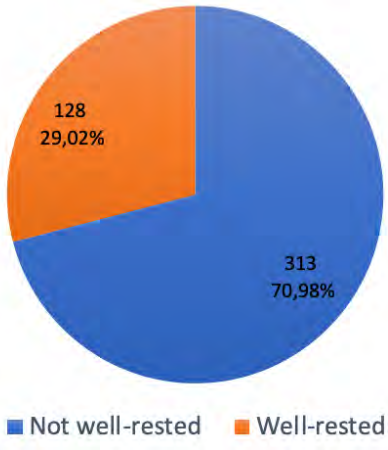


Figure 2. Feeling of rest during remote classes among students

In the surveyed group, 335 (75,96%) persons answered that they feel constantly tired duringthe day. The other 106 persons (24,04%) answered that they do not feel tired during the day (Fig. 3).

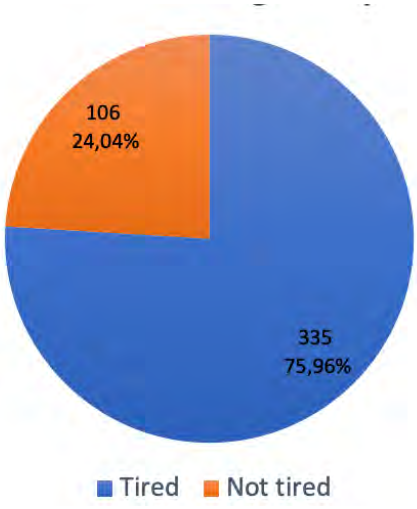


Figure 3. Feeling tired during the day among students

What's more, 65,53% (289) of respondents pointed out that they undersleep on a daily basis.The other 34,47% (152) of them denied that they undersleep every day (Fig. 4).

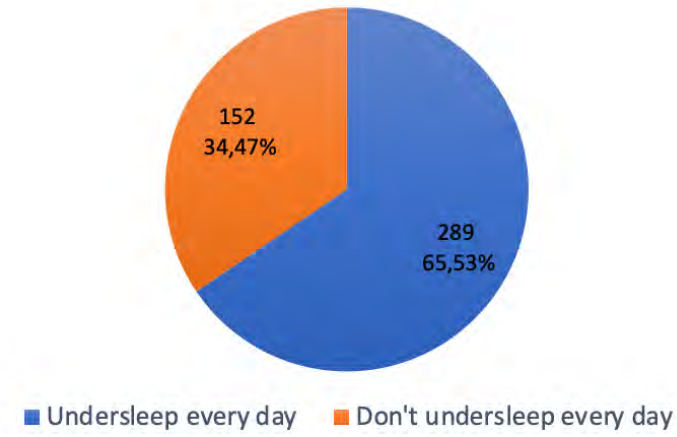


Figure 4. Getting enough sleep every day by students that study remotely

The next few questions were related to taking naps. 152 (34,47%) students answered that theytake naps during homeschooling. Whereas 121 (27,43%) of them had been taking naps before they needed to study remotely. That difference appears to be statistically significant (p= 0,0098).

73 of 152 (48,03%) surveyed that currently take naps admitted that the number of taken naps in a day had increased in comparison to the situation before home schooling. 38 (25,00%) students pointed out that they take less naps then before home schooling. The other 41 (26,97%) students did not notice any change in the number of naps before and during remote classes. That difference is statistically significant (p=0,0235).

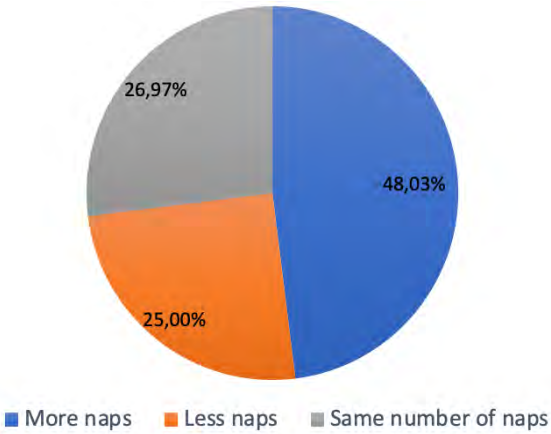


Figure 5. Change in the number of taken naps among students that currently take naps in comparison to that number from before the beginning of homeschooling

In the further question, we wanted to see if students suffer from any sleep trouble, and if so, what their complaints are. 59,41% of surveyed that is 262 people, admitted that they have different sleep troubles. The most common, with 190 (43,08%) answers, are difficulties

in falling asleep. The second in terms of the amount is waking up during the night- 131 students (29,71%) pointed out that answer. Other complaints are: insomnia - 104 (23,59%), excessive sleepiness - 102 (23,13%), excessive sweating during the night- 70 (15,87%), nightmares – 57 (12,92%), sleep terrors - 47 (10,66%) and nycturia - 27 (6,12%) – Fig. 6.

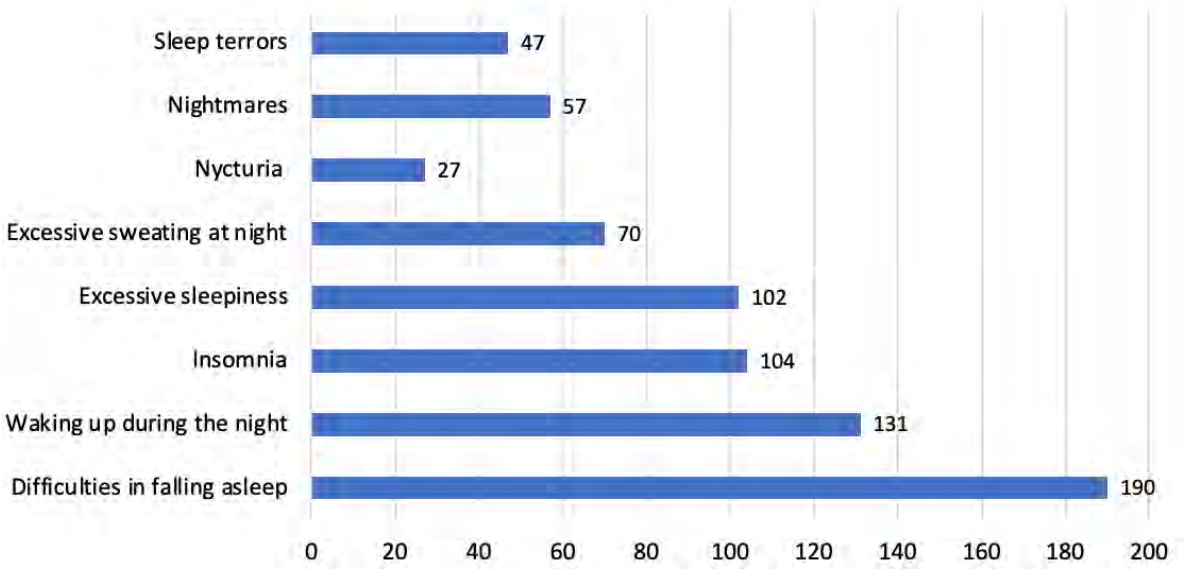


Figure 6. Variety and amount of sleep complaints among students that suffer from any sleep trouble

` 230 (52,15%) respondents answered that they sleep longer in comparison to their average length of sleep before the SARS-CoV-2 pandemic outbreak. Conversely, 151 (34,24%) students answered that they sleep shorter, and the other 60 (13,61%) students admitted that their length of sleep did not change. The difference in the length of sleep that occurred after the SARS-CoV-2 pandemic outbreak is statistically insignificant (p=0,0491) – Fig. 7.

We decided to check if the difference in sleep length is correlated to the change in the numberof naps. The results are as follows:

- Among 151 students that sleep shorter, there are 67 that take the same number ofnaps, 38 that take less naps, and 29 that take more naps than before the remotestudying
- Among 230 students that sleep longer, there are 85 who take the same number ofnaps, 47 that take less naps, and 38 that take more naps than before the remotestudying

There is a statistical correlation between changes in sleep length and in the number of naps that occured after the beginning of homeschooling (p=0,0001).

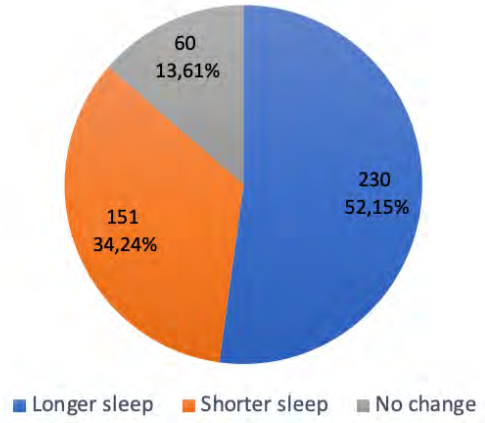


Figure 7. Change in the length of sleep among students in comparison to their length of sleep from before the beginning of remote studying

We wanted to see if the difficulties in falling asleep are related to the changes in the length of sleep. The results are as follows:

- Among 190 respondents that have difficulties in falling asleep, there are 103 that sleepshorter and 87 that sleep the same amount of time or more in comparison to the lengthof sleep from before homeschooling

There is a statistical correlation between having difficulties in falling asleep and shortened time of sleep (p= 0,00005).

Discussion

During the SARS-CoV-2 pandemic, the lack of a routine of leaving home to school may significantly disturb the rhythm of the students' including the balance between work and rest. For the organism of a young person, sleep plays an extremely important role in maintaining health as well as in the learning process and cognitive development [9].

The consequences of deteriorating sleep quality include inattentiveness, reduced executive functioning, and worse results at school [10]. Moreover, sleep impacts the immune system [9], which is so significant nowadays during the SARS-CoV-2 pandemic.

Our study wanted to check how the pandemic and its consequences, such as school closing or online learning, influenced students' sleep behaviour. The study covered 441

students from primary schools and high schools, from big cities, small cities, and villages.

The study results showed that almost three fourth (74,39%) of respondents had experienced a change in sleep quality since online school has begun, which is a significant percentage. This shows that the problem is worth considering. It is important to remember that many studies have suggested that the psychological burden caused by COVID-19 was seen in other pandemic situations, such as the response of young Chinese individuals during the SARS outbreak of the Influenza A (H1N1) outbreak [11]. Therefore psychologicalhealth decline in children during health crises is not a new problem. The long-term effects of staying at home continuously have heightened hysteria and paranoia due to the lack of stimulation inside a home. A sharp uptick in the number of accidental injuries and suicides has been reported in younger individuals during school closures, indicating their profound impact on children's mental health [12].

In the next questions, we asked the respondents whether their quality of sleep had deterioratedor improved. Of the 328 students, 208 reported that their sleep quality has changed for the worse (63,41%). What is more, 188 out of the 208 above do not feel well-rested during online classes. Generally, 70,98% of respondents feel sleepy during lessons, 75,96% feel tired during the day, and 65,53% feel tired every day. These results suggest that the quality of sleep is not satisfactory for most students from the surveyed group. Sleep is a reversible behavioral state characterized by disconnection with the environment while the body relaxes. Therefore, the factors itdisrupts should be eliminated from affecting growing individuals. Sleep is an active processrelated to multiple functions. At the birth of the dream, Active sleep (REM) is longer thanpassive sleep but gradually decreases with age. Therefore those formative years have asignificant role in adult life [13].

We asked students whether they take more or less naps than before the pandemic in the next few questions. 34,47% of students answered that they take naps during homeschooling.In contrast, 27,43% of them had been taking naps before they needed to study remotely. That difference appears to be statistically significant (p= 0.0098).

73 of 152 (48,03%) surveyed who currently take naps admitted that the number of taken naps in a day had increased compared to the situation before homeschooling. On the other hand, 38 (25%) students took less naps than before homeschooling. The other 41 (26,97%) students did not notice any change in the number of naps before and during remote classes. That difference is statistically significant (p=0.0235). Thus, we can conclude that homeschooling influenced students' nap behaviour.

Students were also asked how many hours per day they sleep. One hundred fifty-one respondents sleep less thanbefore the pandemic, 230 sleep more than before the pandemic, and for 60 of them, sleep duration has not changed. The difference in the length of sleep is statistically significant (p=0,0491). Therefore, we can say that homeschooling has affected the amount of sleep of the respondents. However, we can not rule out that this is a factor contributing to the deterioration of their sleep quality.

We decided to check if the difference in sleep length is correlated to the change in the numberof naps. There is a significant statistical correlation between sleep length changes andthe number of naps that occurred after the beginning of homeschooling (p=0.0001). Students who sleep less during the night take more naps during the day.

Finally, we wanted to see if the difficulties in falling asleep are related to the changes in the length of sleep. There is a statistical correlation between having difficulties in falling asleep and changes in the length of sleep.

Our results show how complex the problem is. It can not be forgotten that the rising problem of the Multisystem Inflammatory Syndrome in Children temporally related to SARS-CoV-2 (PIMS-TS) is, consistent with the current state of knowledge. This post-infectious hyperinflammatory immune reaction overlaps with the Kawasaki and toxic shock syndromes. Usually, MIS-C manifests itself 2–4 weeks after a symptomatic or asymptomatic SARS-CoV-2 infection through excessive fever, infection laboratory, and multi-organ involvement. Preceding SARS-CoV-2 infection can usually be identified serologically or suspected based on confirmed exposure. Immunoglobulins and likely corticosteroids and ASS are used therapeutically.

In most cases, intensive therapy isrequired, frequently with catecholamines and every so often with ventilation. Unattended deaths had been described. Mostly there is complete healing; in a few cases, however, brief residual signsor lasting consequential damage persist [14].

This growth in the popularity of disease can give us some answers about problems with children's sleeping patterns. PIMS-TS can be connected to neurological changes, therefore, can createsleeping disorders [15].

Different studies show that poor sleep can be correlated with mental health and behavioural problems [16,17]. For example, antisocial behaviour, depressive symptoms, ADHD-related behaviour and even suicide are associated with sleep problems, overall screen time, mobile phone dependency, and digital device night use [16]. Undoubtedly children are

more likely to be exposed to these factors when learning remotely than when learning in person. This has negative psychological consequences and creates risk factors for a number of physical diseases like obesity, high blood pressure, and Insulin Resistance [16,18].

Insufficient sleep can be related to externalizing and internalizing behavioral problems and deficits in higher-order and complex cognitive functions [17].

Our results show that 29,71% of respondents experience waking up during the night. It can bea result of insufficient sleep depth or altered sleep continuity. These sleep alterations were evidenced in plenty of mental disorders like anxiety, autism, schizophrenia, depression, affective or borderline, and antisocial personality disorders. Sleep continuity disturbances may impact the pathogenesis of mental health disorders because of the nonspecific imbalance that they cause in the arousal system [19].

High levels of physical activity, low levels of sedentary behaviour, and sufficient sleep are thecomponents of an interesting 24-Hour Movement Guidelines for Children and Youth introduced in Canada and Australia to provide a healthy lifestyle for people aged 5-17. Findings indicated a benefit on children's mental health when meeting these recommendations. Moreover, recommendations about sufficient sleep and low levels of sedentary behaviour appeared to be associated with more mental health benefits than the physical activity recommendation [20]. It shows that insufficient sleep and high levels of sedentary activities during homeschooling do not allow students to live a healthy lifestyle.

Another critical issue is the situation in children's homes. Underprivileged children havean increased risk of becoming victims of violence and abuse. This can make children more vulnerable to depression, anxiety, and other mental problems [21]. We assume that it can also result in various sleeping problems. In the survey, we did not ask about the situation inrespondents' homes; that is why we cannot rule out the possibility of domestic problems as the main reason for the decreased quality of sleep among surveyed students.

Conclusions

- For the young organisms, sleep plays an extremely important role in maintaining health as well as in the learning process.
- Homeschooling has significantly affected the quality of sleep of Polish students.
- Almost 75% of the surveyed students experienced a change in sleep quality compared to the state before the pandemic.

- The quality of sleep is not satisfactory for the majority of students from the surveyed group.
- The number of naps among students has changed significantly during remote classes.
- Homeschooling has affected the amount of sleep of the respondents. Therefore, we can not ruleout that this is a factor contributing to the deterioration of their sleep quality.
- Homeschooling influenced students' nap behaviour.
- Multisystem Inflammatory Syndrome in Children temporally related to SARS-CoV - 2can be connected to neurological changes and create sleeping disorders.
- Poor quality of sleep can be correlated with mental health and behavioural problems.
- Sleep continuity disturbances may have an impact on the pathogenesis of mental health disorders.
- Insufficient sleep and high levels of sedentary activities during homeschooling do not allow students to live a healthy lifestyle.
- We have to be aware that domestic problems also may affect the quality of sleep of children.
- Caring about the mental state of children should be a priority.

References

1. Rozporządzenie Ministra Edukacji Narodowej z dnia 11 marca 2020 r. w sprawie czasowego ograniczenia funkcjonowania jednostek systemu oświaty w związku z zapobieganiem, przeciwdziałaniem i zwalczaniem COVID-19.
2. Rozporządzenie Ministra Edukacji Narodowej z dnia 3 czerwca 2020 r. zmieniające rozporządzenie w sprawie czasowego ograniczenia funkcjonowania jednostek systemu oświaty w związku z zapobieganiem, przeciwdziałaniem i zwalczaniem COVID-19.|
3. Bezpieczny powrót do szkół. Działania MEN w zakresie organizacji roku szkolnego 2020/2021 w warunkach epidemii - Ministerstwo Edukacji i Nauki - Portal Gov.pl: https://www.gov.pl/web/edukacja-i-nauka/bezpieczny-powrot-do-szkol-dzialania-men-w-organizacji-roku-szkolnego-20202021-w-warunkach-epidemii (data pobrania: 12.05.2021).
4. Rozporządzenie Rady Ministrów z dnia 23 października 2020 r. zmieniające rozporządzenie w sprawie ustanowienia określonych ograniczeń, nakazów i zakazów w związku z wystąpieniem stanu epidemii.

5. Rozporządzenie Ministra Edukacji i Nauki z dnia 29 kwietnia 2021 r. w sprawie czasowego ograniczenia funkcjonowania jednostek systemu oświaty w związku z zapobieganiem, przeciwdziałaniem i zwalczaniem COVID-19 | Enhanced Reader:
6. Staller N., Randler C.: Changes in sleep schedule and chronotype due to COVID-19 restrictions and home office. Somnologie, 2020, 17, 1-7.
7. Wright K.P., Linton S.K., Withrow D., Casiraghi L., Lanza SM., Iglesia H de la., Vetter C., Depner C.M.: Sleep in university students prior to and during COVID-19 Stay-at- Home orders. Current Biology, 2020, 30(14), R797–R798.
8. Majumdar P., Biswas A., Sahu S.: COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. Chronobiology International, 2020, 37(8):1191-1200.
9. Bruce E.S., Lunt L., McDonagh J.E.: Sleep in adolescents and young adults. Clinical Medicine, Journal of the Royal College of Physicians of London, 2017, 17(5), 424–428.
10. Owens J.A., Weiss M.R.: Insufficient sleep in adolescents: Causes and consequences. Minerva Pediatrica, 2017, 69(4), 326–336.
11. Huang Y., Zhao N.: Chinese mental health burden during the COVID-19 pandemic. Asian Journal of Psychiatry, 2020, 51, 102052.
12. Snape M.D., Viner R.M.: COVID-19 in children and young people. Science, 2020, 6, 370(6514), 286-288.
13. Rana M., Riffo Allende C., Mesa Latorre T., Astorga K.R., Torres A.R.: Sleep in children: physiology and update of a literature review. Medicina (Buenos Aires), 2019, 79, 25–8.
14. Riphagen S., Gomez X., Gonzalez-Martinez C., Wilkinson N., Theocharis P.: Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet, 2020, 395(10237), 1607–1608.
15. PICS Statement regarding novel presentation of multi-system inflammatory disease - Paediatric Critical Care Society: https://pccsociety.uk/news/pics-statement-regarding-novel-presentation-of-multi-system-inflammatory-disease/ (data pobrania: 12.05.2021).
16. Lissak G.: Adverse physiological and psychological effects of screen time on children and adolescents: Literature review and case study. Environmental Research, 2018, 164,149–157.

17. Astill R.G., Heijden K.B., Van Ijzendoorn M.H., Someren EJW Van: Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed. Psychological Bulletin, 2012, 138(6), 1109–1138.
18. Domingues-Montanari S.: Clinical and psychological effects of excessive screen time on children. Journal of Paediatrics and Child Health, 2017, 53(4), 333–338.
19. Baglioni C., Nanovska S., Regen W., Spiegelhalder K., Feige B., Nissen C., Reynolds C.F., Riemann D.: Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychological Bulletin, 2016, 142(9), 969–990.
20. Sampasa-Kanyinga H., Sampasa-Kanyinga H., Colman I., Colman I., Goldfield G.S., Goldfield G.S., Janssen I., Wang J., Wang J., Podinic I., Podinic I., Tremblay M.S., Saunders T.J., Sampson M., Chaput J.P., Chaput J.P.: Combinations of physical activity, sedentary time, and sleep duration and their associations with depressive symptoms and other mental health problems in children and adolescents: A systematic review. International Journal of Behavioral Nutrition and Physical Activity, 2020, 17, 72.
21. Singh S., Roy D., Sinha K., Parveen S., Sharma G., Joshi G.: Impact of COVID-19 andlockdown on mental health of children and adolescents: A narrative review with recommendations. Psychiatry Research, 2020, 293, 113429.

Knowledge among medicine and dentistry students of Poland about COVID-19 guidelines

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Abbreviation list

- COVID-19- coronavirus disease 2019
- SARS-CoV-2- severe acute respiratory syndrome coronavirus 2 PPE- personal protective equipment

Introduction

2020 pandemic challenged the health system all around the world. It was the biggest test to health workers, their knowledge and ability to adapt to changing situations. Furthermore, countries and health organizations had to publish acceptable guidelines to help in a crisis. Celebrating one year of the pandemic, we checked medicine Students in Poland knowledge about them. Those students will soon be front workers with Corona patients, so they need to be equipped with the knowledge and practical skills to fight for the lives of new generations of patients.

What is COVID-19?

Coronavirus causes diseases in animals and humans all over the world. It is known thathuman coronavirus (HCoV) mainly causes upper and lower respiratory tract

infections. However, symptoms can also affect the nervous and digestive systems. This is the SARS- CoV-2 epidemic, originally called 2019-nCoV. The most common symptoms are fever and cough, fatigue, phlegm, shortness of breath, myalgia, joint pain or sore throat, headache, nausea, vomiting, or diarrhea (30%). The best preventive measure is to avoid pollution. In addition, the contact person must assume the obligation of isolation. Patients with COVID-19 should receive treatment in specialized centers. A large number of patients with pneumonia require passive oxygen therapy. Non-invasive ventilation and high-flow nasal oxygen therapy can be used for mild to moderate patients without hypercapnia. Patients with acute respiratory distress syndrome and mechanical ventilation should adopt economic ventilation strategies. Extracorporeal membrane oxygenation is a highly specialized method available inselected centers and is not suitable for many situations. There is currently no specific drug treatment for COVID-19. Modern medicine is preparing to fight the new coronavirus pandemic. This is a holistic approach for patients, mainly involving the use of personal protective equipment to reduce the risk of further spread of the virus and patient management, including isolation and patient management (including treatment) without specific pharmacological symptoms or treatment and symptomatic treatment [1].

The virus has spread to almost all of the world and as of May 1, 2021 there were confirmed cases of infection and deaths. Coronavirus information is updated daily. This data shows how enormous a problem this pandemic is pretending to health care workers in Poland and all around the world.

COVID-19 Procedures around the world

The best prevention is to avoid exposure to the virus. In addition, contact persons must be subject to an obligation to quarantine. However, this is not possible for medical personnel, which must be equipped with special personal protective equipment. Airborne precautions and other protective measures were discussed and suggested for prevention [2].

The proper use and disposal of masks are essential to avoid an increased risk of transmission [3,4].

Infection prevention and control measures that may reduce the risk of exposure include use of face masks, covering coughs and sneezes with tissues, which are then safely disposed of, regular handwashing with soap or hand sanitizer, disinfectants with at least 60% alcohol, avoiding contact with infected people and keeping a reasonable distance and not touching the

eyes, nose and mouth with unwashed hands. While infected individuals should wear masks to reduce the risk of infecting others, medical personnel should be equipped with particle aspirators such as certified N95 or FFP2 when performing aerosol generation procedures and using medical devices. Masks in the treatment of suspected or confirmed cases [5]. According to WHO guidelines on using masks in the community, during home care, and healthcare-related to the novel coronavirus 2019-nCoV [4], people with respiratory symptoms should wear medical masks. Tract infection accordingly. People without respiratory symptoms are not required to wear medical masks in public, although more and more experts are questioning this claim. If an infection is suspected, both emergency teams and medicaldispatchers must use specific management algorithms. Management can accordingly be divided into two main types. Suppose upper respiratory tract infection symptoms are observed without shortness of breath and at temperatures below 38 degrees Celsius. In that case, the patient should be moved to isolation and wait for the test result or a hospital specializing in infectious diseases. These departments or hospitals must also be selected for patients with shortness of breath, coughing, and temperatures above 38 degrees Celsius, including those in severe conditions with concurrent illnesses that require intensive medical supervision. The medical service staff will perform procedures where you may only suspect coronavirus infection based on an examination and interview. After transportation, the ambulance must bedisinfected with a wide range of disinfectants.

Aim

The study aimed to compare the knowledge of students of Polish medical universities about COVID guidelines.

Materials and methods

The research group consisted of 89 students of medical and dentistry faculties from several universities in Poland. 64% of the respondents were students of the Wrocław Medical University, 13,5% of the Silesian Medical University, 3,4% of the Medical University of Bialystok. The remaining 19,1% were students of other medical universities. The vast majority (92,1%) of the respondents were students of the Faculty of Medicine; the remaining 7,9% were students of the Faculty of Dentistry. 42,7% had infectious diseases classes during

The pandemic, while 23,6% had classes before, 33,7% of the respondents did not yet have classes of infectious diseases. The majority of the respondents were students of the five year- 38,2%, the second in terms of size were the 4-year students - 19,1%, then 1st year - 14,6%, 3rd year - 11,2%, then 2nd year - 9% and 6th year- 7,9%. The research was carried out using the original questionnaire created by the authors, containing eight questions regarding students' knowledge on the issuing regulations concerning behavior during the COVID pandemic. The survey was conducted online using Google Forms. Inclusion the survey held the status of a Faculty of Medicine or Dentistry student in the medical university of Poland.

Results

This part of the work will present the results of the survey. In the survey, we asked students what the conduct algorithm in case of suspecting COVID-19 is—Figure 1.

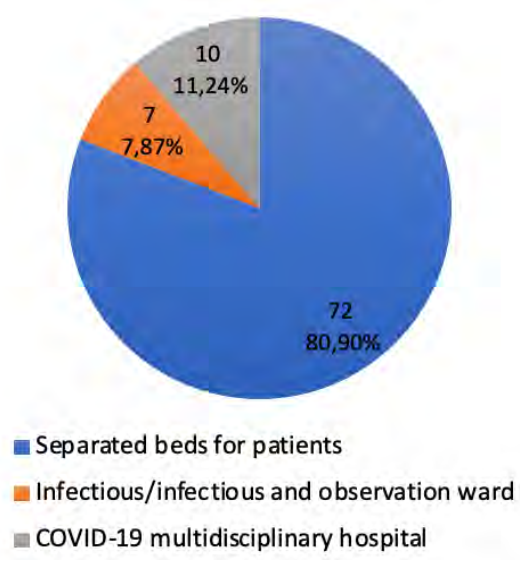


Figure 1. Shows the students' answers to the question of what the expression "first degree of protection" in the algorithm of conduct in case of suspecting COVID-19 means

80.9% (72) of respondents answered correctly what the first degree of protection means and pointed out separate beds for patients. The other 19.1% (17) of respondents pointed out incorrect answers, that is, infectious or infectious and observation ward (7) and COVID-19 multidisciplinary hospital (10).

The expression "second degree of protection" in the same algorithm means an infectious or infectious observation ward. Seventy-six students pointed out that answer that is 84,4% of all respondents. 10,1% (9) surveyed pointed out that the second degree of protection

means separated beds, and the last 4,5% (4) answered that it means COVID-19 multidisciplinary hospital. Both of the above are incorrect answers. The results are shown on Figure 2.

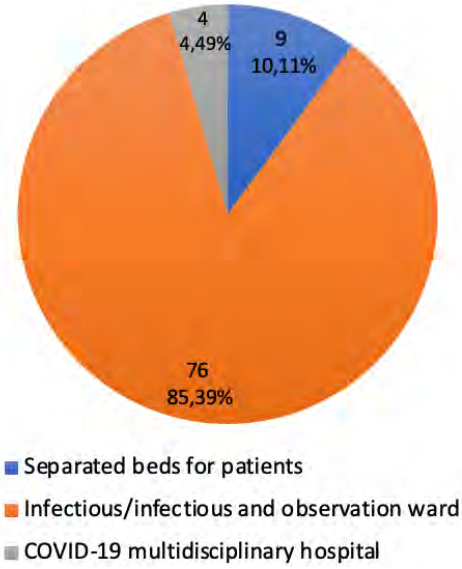


Figure 2. Shows the students' answers to the question of what the expression "second degree of protection" in the algorithm of conduct in case of suspecting COVID-19 means

In the surveyed group, 74 (83.2%) persons answered correctly that the third degree of protection in the mentioned algorithm means a COVID-19 multidisciplinary hospital. However, the other 15 students gave incorrect answers and pointed out separated beds for patients (10) and infectious or infectious and observation ward (5). Figure 3 presents these results.

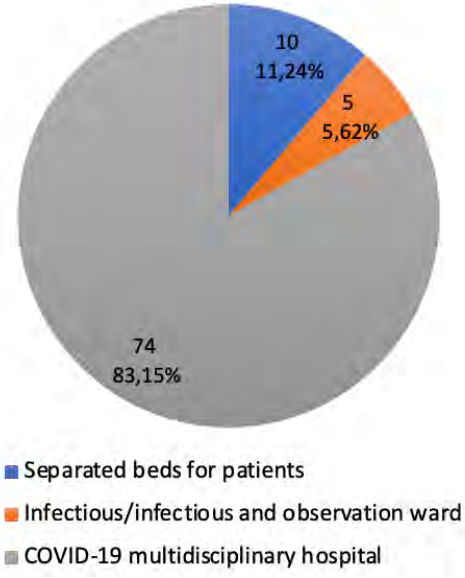


Figure 3. Shows the students' answers to the question of what the expression "Third degree of protection" in the algorithm of conduct in case of suspecting COVID-19 means

In the other part of the study, we asked respondents to point out which special personal protective equipment should be used by the health care workers when contacting different patients.

According to the guidelines of the Polish Ministry of Health, the medical personnelin contact with a healthy person or a patient without symptoms of respiratory tract infection should always be equipped with as minimum: a surgical mask, medical clothing or a fleece apron, and disposable gloves when the procedure requires it. Moreover, it is mentioned to pay more attention to hand hygiene. These answers were pointed out by 77 (86,5%), 66 (74,1%), 36 (40,4%), 69 (77,5%) and 82 (92,1%) respondents respectively as it is shown in Figure 4.

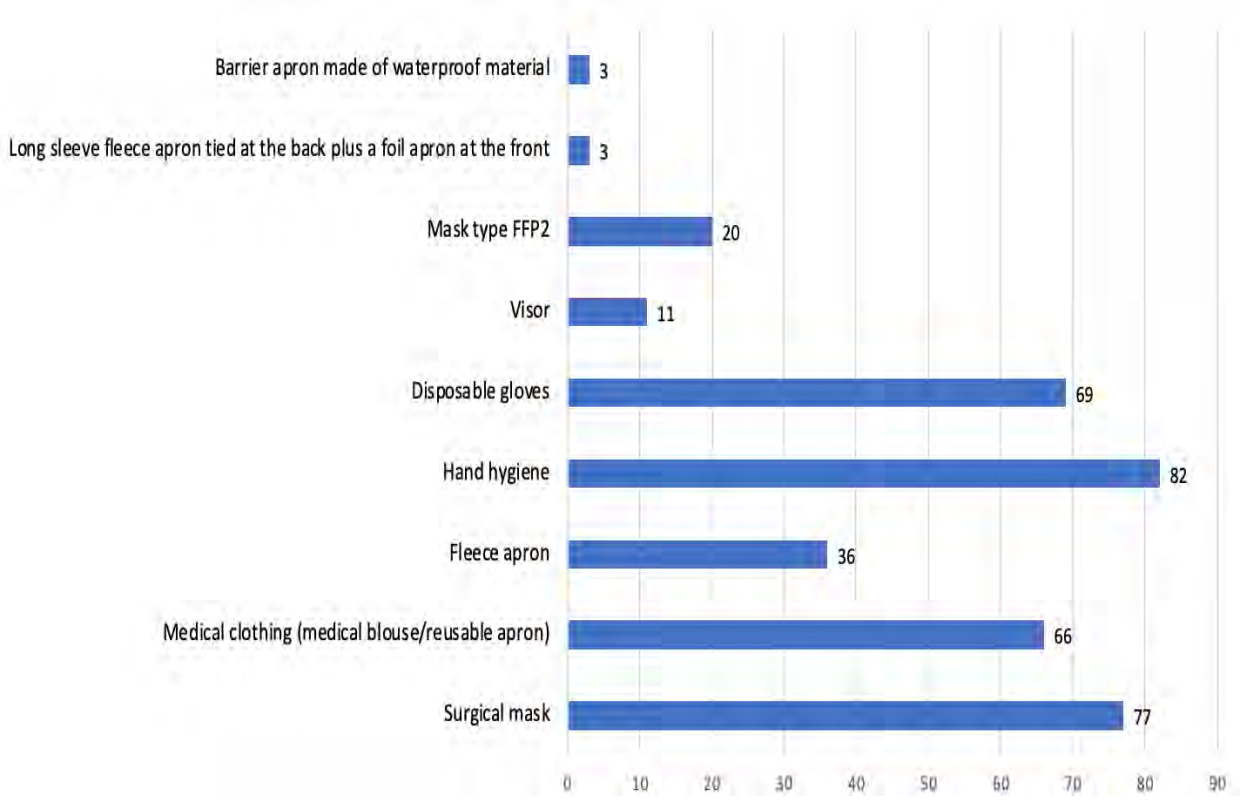


Figure 4. Shows the students' answers to the question of what equipment is needed when contacting a healthy person or a patient without any symptom of respiratory tract infection

The forms of protective equipment mentioned in other answers are unnecessary: a visor, a mask type FFP2, a long sleeve fleece apron tied at the back plus a foil apron at the front, and a barrier apron made of waterproof material. These answers were pointed out by11 (12,4%), 20 (22,5%), 3 (3,4%) and 3 students respectively.

In case of contact with a patient with symptoms of respiratory tract infection with the

riskof aerosol formation, the required protective equipment is always as a minimum: a mask type FFP2 and a visor, a long sleeve fleece apron tied at the back, plus a foil apron at the front, or a barrier apron made of waterproof material and disposable gloves. These answers were pointedout by 78 (87,6%) and 66 (74,2%), 41 (46,1%), 20 (22,5%) and 79 (88,8%) respondents respectively. The other answers were related to equipment that is insufficient in contact with this type of patient: hand hygiene with 73, a fleece apron with 51, medical clothing with 63, and a surgical mask with 35 answers. Precise results are shown in Figure 5.

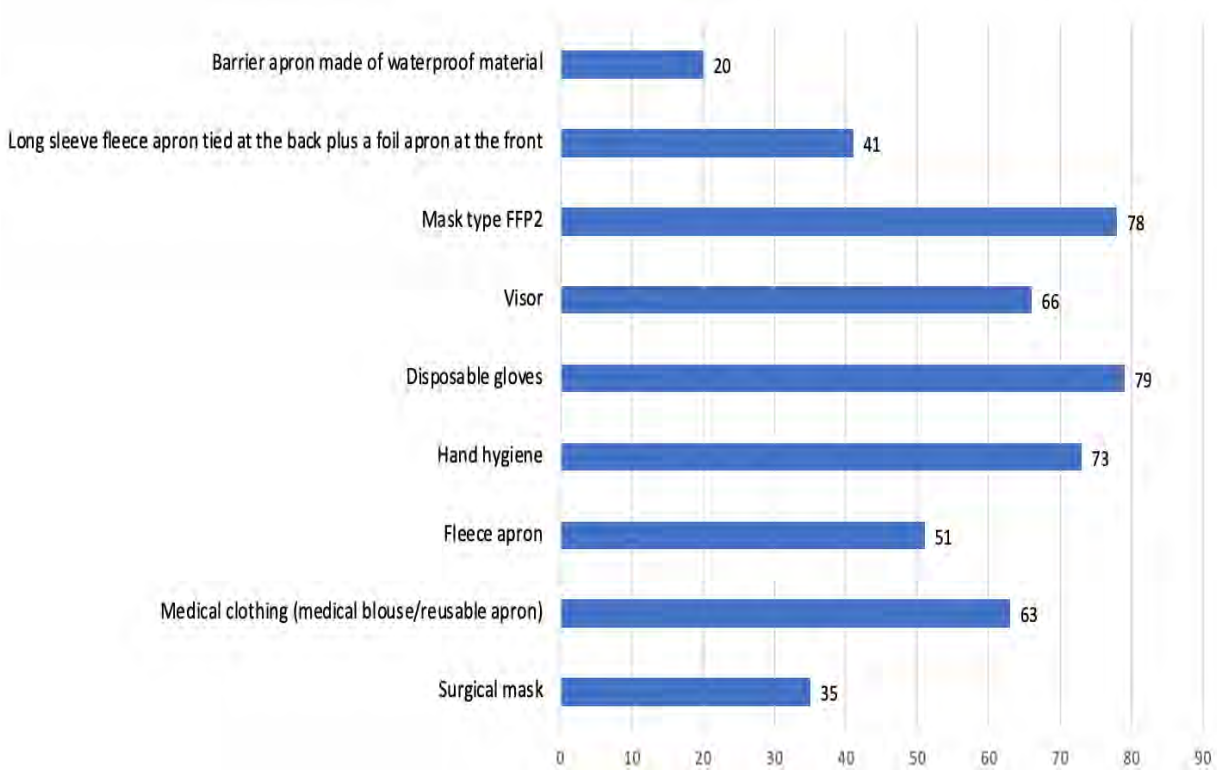


Figure 5. Presents the surveyed answers to the question of what equipment is needed when contacting a patient with symptoms of respiratory tract infection with the risk of aerosol formation

In the next question, we wanted to check the students' knowledge about the type of room in which patients infected with SARS-CoV-2 should be isolated. The correct answer, which is a single room with full sanitary facilities including a toilet and a bathroom, was pointed out bya vast majority of students- 79,55%. Unfortunately, the other 20,4% of respondents marked wrong answers: a dormitory room with full sanitary facilities 18,15% and a single room without full sanitary facilities- 2,25%. These results are presented in Figure 6.

We asked students how often cleaning and disinfection in an isolation room should be

performed in the penultimate question. The correct answer is once a day and always in the eventof biological contamination, and it was pointed out by the majority of respondents- 61,8%. 14,6% surveyed answered that cleaning and disinfection in an isolation room should occur once a day, regardless of events of biological contamination during the day, 19,1% answered two times a day, 3,4%- every two days and 1,1%- once a week. All of the above are incorrect answers. Details are shown in Figure 7.

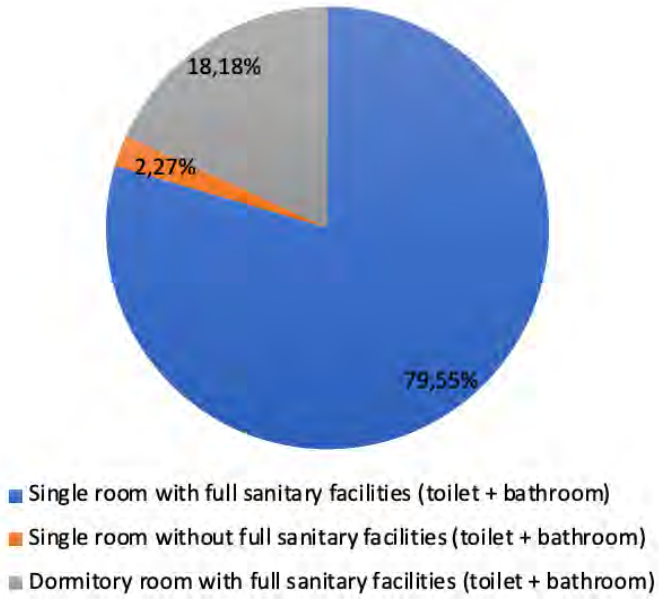


Figure 6. Shows the students' answers to the question of in what type of room patients infected with SARS-CoV-2 should be isolated

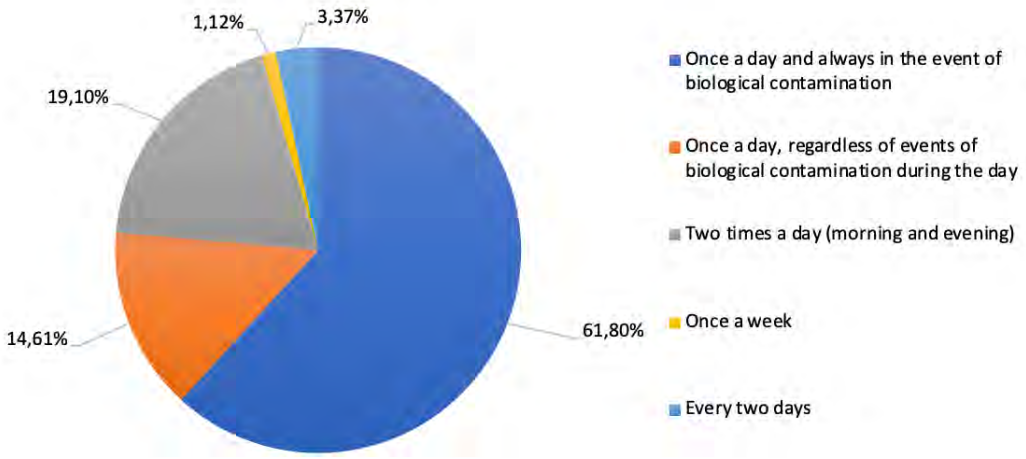


Figure 7. Presents students answers to the question of how often cleaning and disinfection in isolation rooms should be performed

In the last question, we wanted to see if students know what ventilation time of an isolation room is required after a patient leaves it. 28,1% (25) of respondents chose the correct answer, which is about 1 hour. 37.1% (33) reported about 30 minutes, and that is an incorrect answer, as well as about 3 hours, chosen by 29,2% (26) surveyed and about 10 minutes 5.6% (2) of respondents. More precise results are shown in Figure 8.

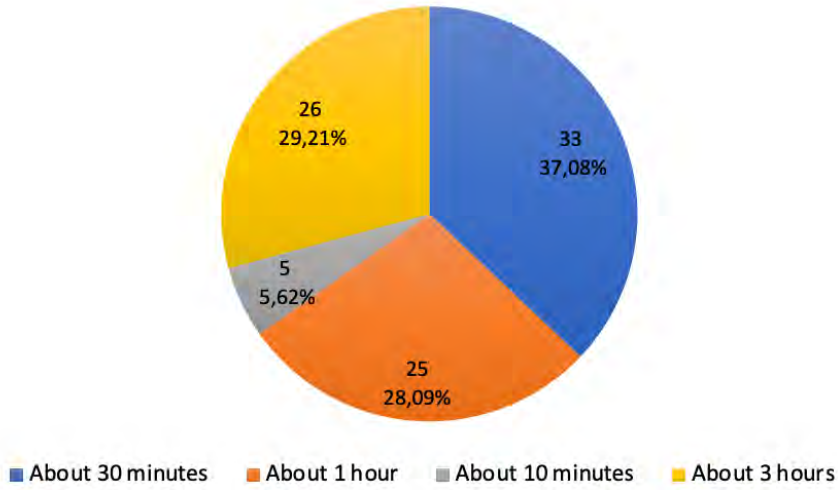


Figure 8. Shows students' answers to the question of what the time of ventilation of an isolation room after a patient leaves it is required

Discussion

The subject of treating patients with COVID is currently a significant problem in the healthcare sector. Nowadays, every doctor is in a frontline meeting and treating ill patients or they are helping recover in her/his medical practice. Therefore, it is essential that students, who graduate from medical universities, have sufficient knowledge on the subject as they start their professional career in medical practice immediately after graduation. Ignorance of the law and guidelines in situations related to the death and illness of another person harms the doctor, the patient, and their family. Therefore, knowledge of legal regulations protects the doctor against spreading disease to other patients and is protecting his health.On the other hand, the patients are protected from getting infected and can recover in the most optimal environment.

Our work aimed to examine the level of knowledge of students of medical universities in Poland on the guidelines considering COVID. The study covered 89 students from various medical universities in Poland.

In the first question, we asked students what the conduct algorithm in case of suspecting COVID-19 is. The study results showed that 80,9% of respondents answered correctly to what the first degree of protection means and pointed out separate beds for patients. The other 19,1% of respondents pointed out incorrect answers.

The expression "second degree of protection" in the same algorithm means an infectious or infectious observation ward. Seventy-six students pointed out that answer that is 84,4% of all respondents. 15,6 % of respondents pointed out incorrect answers.

In the third question, 83,2% of persons answered correctly that the third degree of protection in the mentioned algorithm means a COVID-19 multidisciplinary hospital. The other 16,8% of students gave incorrect answers.

After analyzing the students' answers to these first three questions, we can say that on the one hand, the results show acceptable awareness of students on the algorithm for dealing with a patient suspected of COVID-19, self-transport [6].

However, on the other hand, students should be familiar with the algorithm for dealing with suspected SARS-CoV2 infection in a patient because it is a critical issue for health care organizations in such a difficult time as a pandemic.

In the other part of the study, we asked respondents to point out which special personal protective equipment should be used by the health care workers when contacting different patients. According to the guidelines of the Polish Ministry of Health [6], the medical personnel in contact with a healthy person or a patient without symptoms of respiratory tract infection should be equipped with as minimum: a surgical mask, medical clothing or a fleece apron and disposable gloves when the procedure requires it. Moreover, it is mentioned to pay more attention to hand hygiene.

In case of contact with a patient with symptoms of respiratory tract infection with the risk of aerosol formation, the required protective equipment is always as a minimum: a mask typeFFP2 and a visor, a long sleeve fleece apron tied at the back plus a foil apron at the front, or a barrier apron made of waterproof material and disposable gloves.

On the one hand, the results from our study show that students present a certain level of knowledge about personal protective equipment (PPE) that should be used by the health care workers when contacting different patients. On the other hand, this knowledge is insufficient given its importance at present. Personal protective equipment is of great importance in preventing the spread of the SARS-CoV2 virus in society. PPE should be appropriately adjusted to the possible way the virus spreads during patient care - contact,

droplet, or airway mode of transmission [7].

In the following question, we wanted to check the students' knowledge about the type of room in which patients infected with SARS-CoV-2 should be isolated. The correct answer, which is a single room with full sanitary facilities including a toilet and a bathroom, was pointed out by a vast majority of students- 79,55%. The other 20,4% of respondents marked wrong answers. That shows that students generally know how infected patients should be isolated.

The last two questions concerned maintaining the isolation rooms in an appropriate state of cleanliness - their washing, disinfection, and airing. In the penultimate question, the majority of respondents - 61,8% - answered correctly that it is required to disinfect the isolation room once a day and always in the event of biological contamination. In the last question, we asked about the duration of the room ventilation after a patient leaves it. The majority - 71,9% - chose the wrong answer. Most of the students did not know that the correctanswer is - about 1 hour of ventilation. The above statistics show that the students aregenerally unaware of the hygiene guidelines for isolation rooms.

Conclusions

- Students of medical universities in Poland know the guidelines considering COVID. However, this knowledge is incomplete and insufficient.
- Universities should provide an appropriate level of infectious diseases classes so that the graduate starts her/his professional career with sufficient knowledge that is necessary for medical practice.
- The intricacy and vagueness of legal acts regarding guidelines considering COVID is a common problem among students and doctors.
- Ignorance of the law and created rules are harmful. Knowledge of legal acts not only protects the doctor against.
- Poland is not the only country struggling with the complexity of guidelines considering COVID.
- In order to improve knowledge, additional classes/updated educational materials on COVID-19 infection and related guidelines should be provided to students who have already passed the exams in infectious diseases before the onset of the COVID-19 pandemic.

- Medical students should represent an adequate level of knowledge of COVID-19 recommendations to share reliable information with others. Educating the public is the key to reducing risky behaviours and thus reducing the spread of the disease.

References

1. Dzieciatkowski T., Szarpak L., Filipiak K.J., Jaguszewski M., Ladny J.R., Smereka J.: COVID-19 challenge for modern medicine. Cardiology Journal, 2020, 27(2), 175–183.
2. Smereka J., Szarpak L., Filipiak KJ.: Modern medicine in the COVID-19 era. Disaster and Emergency Medicine Journal, 2020, 5(2), 103–105.
3. Szarpak L., Smereka J., Filipiak K.J., Ladny J.R., Jaguszewski M.: Cloth masks versus medical masks for COVID-19 protection. Cardiology Journal, 2020, 27(2), 218–219.
4. Advice on the use of masks in the community, during home care and in healthcare settings in the context of the novel coronavirus (COVID-19) outbreak: https:// www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak (data pobrania: 14.05.2021).
5. Wax R.S., Christian M.D.: Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Canadian Journal of Anesthesia, 2020, 67(5), 568–576.
6. Wytyczne dla poszczególnych zakresów i rodzajów świadczeń - Ministerstwo Zdrowia Portal Gov.pl: https://www.gov.pl/web/zdrowie/wytyczne-dla-poszczegolnych-zakresow-i-rodzajow-swiadczen?fbclid=IwAR0K8ziGeTuRftdgJKuS_RW9pJzlZ4oWdH7yKMylV 8e6Zxi14 Pz86HOWfnE (data pobrania: 12.05.2021).
7. Cook T.M.: Personal protective equipment during the coronavirus disease (COVID) 2019 pandemic – a narrative review. Anaesthesia, 2020, 75(7), 920–927.

Out of hospital cardiac arrest during the COVID-19 pandemic; the challenges emergency medical services must face

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Abbreviation list

- AED - automatic external defibrillator
- CPR - cardiopulmonary resuscitation
- ECG - electrocardiography
- EMS - emergency medical services
- OHCA - out-of-hospital cardiac arrest
- OR - termination of resuscitation
- PPE - personal protective equipment
- ROSC - a return of spontaneous circulation
- SCD - sudden cardiac death
- SHD - survival to hospital discharge

Introduction

It seems that out-of-hospital cardiac arrest (OHCA) has gained much significance during the COVID-19 pandemic we are still facing. Over the past year, there has been a rapidly increasing number of studies from all over the world trying to establish a relation ship between the expanding incidence of OHCA occurrence with growing OHCA death rate and the onset of

COVID-19 pandemic. Many different factors supporting this relation ship might have come into play: the changing etiology of cardiac arrest, the shift of OHCA location with predominance at home and less

t on the streets, the change in people's attitude towards providing first aid as well as availability together with efficiency of emergency medical services (EMS) [1].

As we can see, the factors may be attributable both to infection- and pandemic-related issues. Concerning infection-related issues: possible respiratory failure caused by SARS-CoV-2(hypoxia and increase in non-shockable rhythms) while considering the pandemic-related issues: social distancing, fear of being infected in the hospital, or the desire not to burden the health system further, both resulting in non-activation of the emergency system [2].

Furthermore, performing cardiopulmonary resuscitation (CPR) in OHCA has become more troublesome than ever. Addressing the potential risk of infection to healthcare workers and lay rescuers due to the potential generation of aerosols, the international societies such as the International Liaison Committee on Resuscitation (ILCOR), American Heart Association (AHA), U.K. Resuscitation Council, and European Resuscitation Council [3] have come up with modified guidelines for resuscitation, which all emphasize the importance of the safety of lay rescuer or professional health personnel, contributing to the paradigm shift in which the rescuer vs. rescuee relationship has been blurred and it's not clear anymore who is the one to be saved.

In this paper, we gather and juxtapose all the research and review works arising over the past year worldwide and analyze the data obtained to establish a relationship between the changes in OHCA patterns and the COVID-19 pandemic.

Materials and methods

The available literature on the subject area has been reviewed with the help of databases such as Google Scholar, ScienceDirect, PubMed by using keywords such as OHCA, COVID-19, EMS, CPR.

Review, analysis

Multifactorial issue

The relationship between the COVID-19 and the excessive OHCA incidence is

multifactorialand includes direct and indirect effects, not all identified yet. The COVID-19 pandemic has tested the efficiency of healthcare systems around the world and has exposed shortages in healthcare resources. In response to hospitals' overload with COVID-19 patients, several changes in the functioning of medical facilities have occurred. These changes included reducing access to preventive care across primary and secondary care, canceling scheduled operations, and reorganizing hospital wards to create beds for infectious patients. In addition, in order to minimize the risk of viral transmission, clinical pathways were redesigned to support telemedicine and limit face-to-face contact between healthcare providers and healthcare recipients. These changes could have limited early accessto healthcare for patients at risk of cardiac arrest.

SARS-COV-2 infections can lead to various serious complications, including hypoxia, myocarditis, and hyper-coagulable state leading to thrombotic events including cerebral vascular accidents or pulmonary embolism, all of which are potential causes of OHCA [1]. Furthermore, it cannot be excluded that some patients experienced arrhythmic sudden cardiac death (SCD) related to the infection. Some drugs used in COVID-19 therapy, such as hydroxychloroquine and azithromycin, might have contributed to the Q.T. interval prolongation with the consequent risk of ventricular arrhythmias. In a study by Baldi et al. four out of six patients of the investigated population with suspected or diagnosed COVID-19and a post-ROSC ECG (electrocardiography) showed a prolonged QTc interval [2].

New recommendations for resuscitation emphasize the necessity to use full PPE (Personal protective equipment) by medical services and put the rescuer's safety first.

All these factors undeniably influenced OHCA patterns, including the increase in occurrence, changes in presentation - more patients presenting in a non-shockable rhythm (90% compared to approximately 80% during non-pandemic times) - and hence a worse outcome [4].

OHCA in Covid-19 vs Non-Covid-19 patients

Data from a meta-analysis by Borkowska et al. [5], which included 5 studies with a total of 4210 patients, show a significantly lower return of spontaneous circulation (ROSC) (13.3% vs. 26.5%, respectively) and survival to hospital discharge (SHD) rate (0.5% and 2.6%, respectively) in COVID-19 patients, compared to non-COVID-19 patients. COVID-19 patients also tend to present shockable rhythms far less often than others (5.7% compared with 37.4% in the non-COVID-19 group). Chances for SHD with favorable neurological outcomes were estimated to be 0% in COVID-19 vs. 3.1% in non-COVID-19 patients. Since CPR is a highly

aerosol-generating procedure, it carries a risk of viral transmission, whichcan discourage bystanders from performing CPR and forces the use of full personal protective equipment (PPE) by medical services. Several studies showed that PPE decreased rescuers' comfort and ability to carry out CPR [6,7].

However, the abovementioned meta-analysis showed that bystander CPR rate and ALS implementation were comparable in both groups. Therefore, it concludes that a decrease in SHD and ROSC in COVID-19 patients is more likely due to the initially more severe state of COVID-19 patients, as indicated by the lower rate of shockable rhythms, and not due to the lower frequency of bystander CPR and ALS implementation.

Comparison of OHCA before and during the pandemic

We analyzed the data collected and elaborated by researchers in Switzerland [8], Lombardy [9], Victoria [10], London [11], Paris [12], Osaka [13], Spain [14], Sweden [15], Multnomah County in Oregon and Ventura County in California [16].

All these studies consisted of comparing the data of the patients with OHCA between two different time periods. One of them was during the COVID-19 pandemic and the other was at the same time a year before the pandemic or data from the first period were compared with data from the years before the pandemic. During the COVID-19 pandemic, a significant increase in the incidence of OHCA was observed in almost all surveyed regions.

The exception is Switzerland, where the incidence of OHCA in regions with a high incidenceof COVID-19 was lower during the pandemic than in the compared period in 2019 [8]. What makes the results from Switzerland even more surprising is that the cohort study on the population of 50 large cities in the United States also indicated a strong correlation between the incidence of COVID-19 and the incidence of OHCA. Moreover, McVaney et al. suggested that sudden escalations in OHCA may also serve as an early foreshadowing or signal of pending COVID-19 surges in communities [17].

A notable group of OHCA patientswas infected with the SARS-CoV-2 virus, e.g., 24.5% of OHCA patients in London, at least 10% of patients in Sweden [11,15].

During the pandemic, cardiac arrest was less frequent in public places than in the pre-pandemic period, which in all regions resulted in less frequent application of the public- access AED pad (Automated External Defibrillator) and a longer time to the first shock as presented in the graph below [Fig. 1].

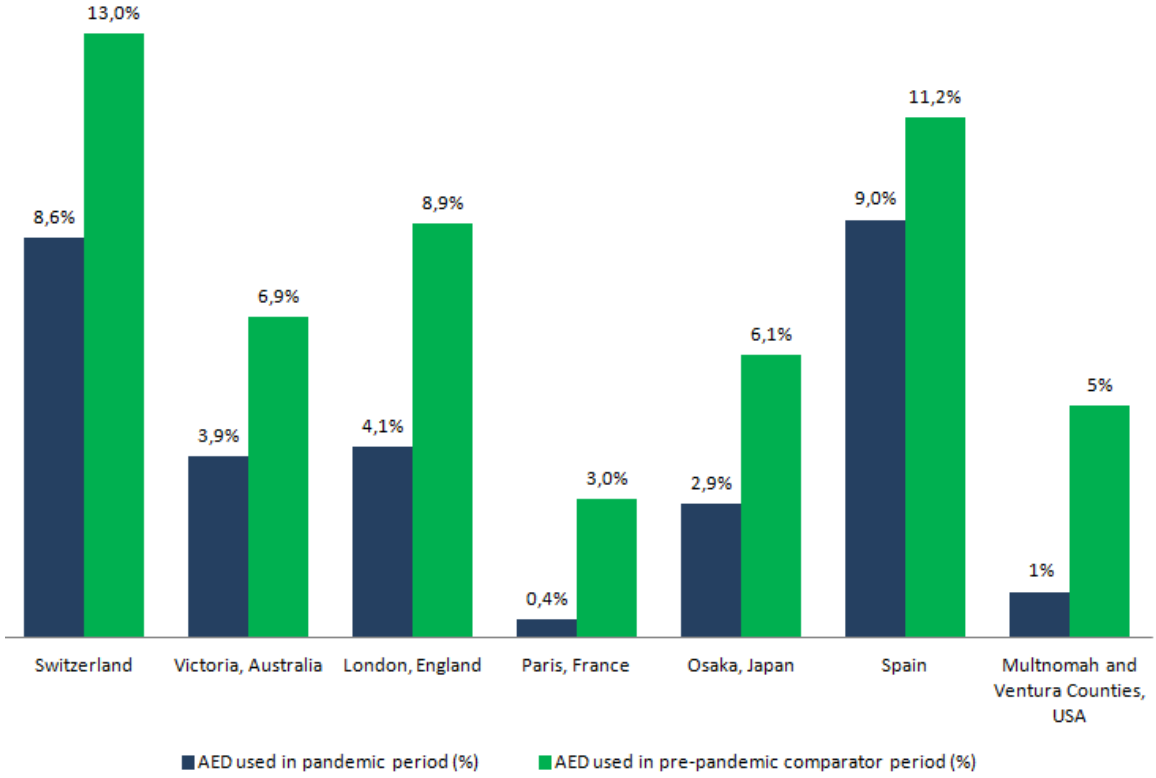


Figure 1. Comparison of AED application in OHCA patients between pandemic and pre-pandemic periods. Source: Authors' own work based on items: 7., 9., 10., 11., 12., 13. and 15. of the bibliography

Bystander CPR

A question arises as to whether bystanders are less willing to resuscitate OHCA during the COVID-19 pandemic. According to Australian researchers, bystander CPR was performed more often during the pandemic than before, possibly because most cardiac arrests occurred at homes with families willing to take the risk [10]. Researchers from London [11] obtained similar results. A higher frequency of OHCA in private residences would also explain the decreased usage of AED and extended median time-to-the-first-shock. Researchers from the United States of America, Italy, Japan, Spain, and Switzerland, on the other hand, obtained opposite results**,** proving that lay rescuers undertookresuscitation activities less frequently than before [8,9,13,14,15,16].

Grunau and co-workers were also looking for answers to the questions as to whether and how the COVID-19 pandemic influenced the willingness of bystanders to undertake resuscitation. They distributed a 12-item survey to the general public via social media in 26 countries. The results showed a decreased willingness to perform bystander CPR towards unfamiliar persons, which was, however, ameliorated if simple PPE were available. Victim age

had a significant impact with respondents being more willing to intervene in pediatric than geriatric cases, which may be due to a balance between potential benefits to the victim (i.e., the elderly may have poor OHCA outcomes). Respondents declared a greater decrease in willingness to undertake rescue breaths and chest compressions than to call 9-1-1 or apply an AED, which may be associated with the risk of SARS-CoV-2 transmission. A decrease in willingness to provide bystander care did not appear correlated with higher regional COVID-19 incidence. Regions with the lowest COVID-19 incidence tended to have the largest decreases in willingness [18].

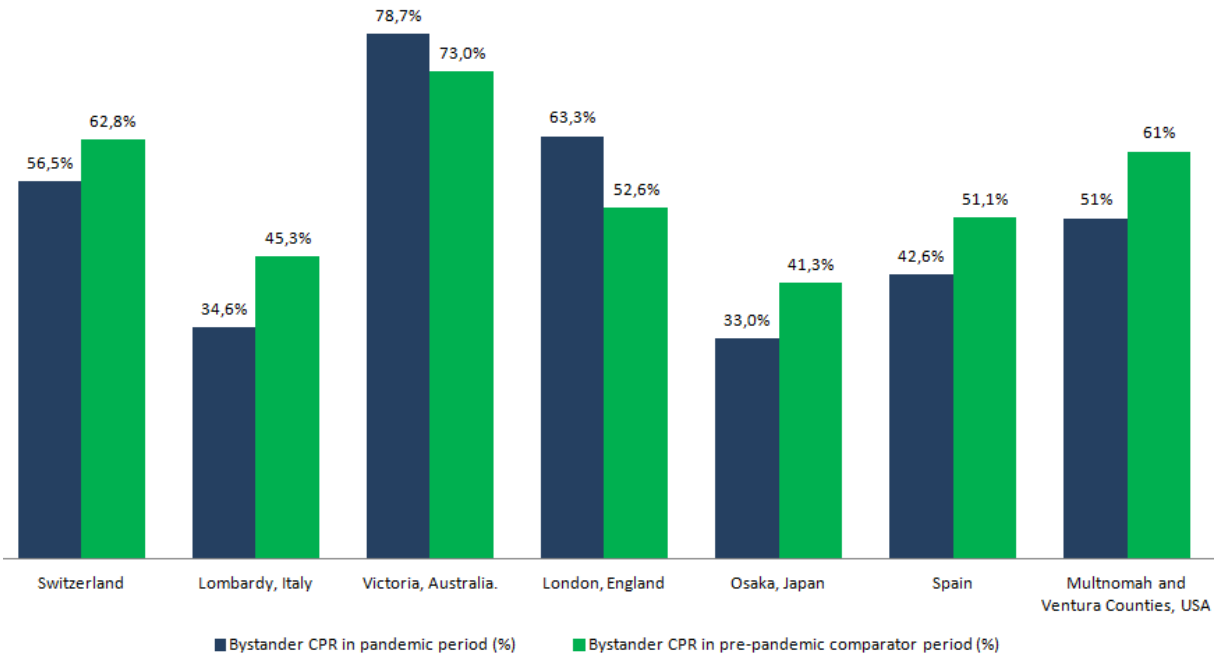


Figure 2. Comparison of CPR initiated by bystanders in patients with OHCA between pandemic and pre-pandemic periods. Source: Authors' own work based on items: 7., 8., 9., 10., 12., 13. and 15. of the bibliography

PPE, necessary but troublesome

A retrospective observational study by Cho et al. conducted on the OHCA patients in Daegu, South Korea, emphasized the importance and preparedness of PPE. As a result, PPE was introduced among all the examined interventions, with standard CPR being changed to chest compressions using mechanical devices. Thanks to the protective measures, the number of medical personnel requiring self-isolation after providing CPR and the number of complete or partial closures of emergency centers has decreased, proving somewhat the effectiveness of implementing PPE [19].

In turn, Borkowska et al. point out in their retrospective cohort study that several other studies showed the negative influence of PPE on rescuer comfort and ability to carry out CPR and the discouragement caused by the risk of viral transmission during the bystander CPR [20].

Overloaded systems

The increased load on emergency medical systems had an impact on the extension of the timepassing from the call being answered by dispatcher to the arrival of the emergency medical team to the scene of the accident.

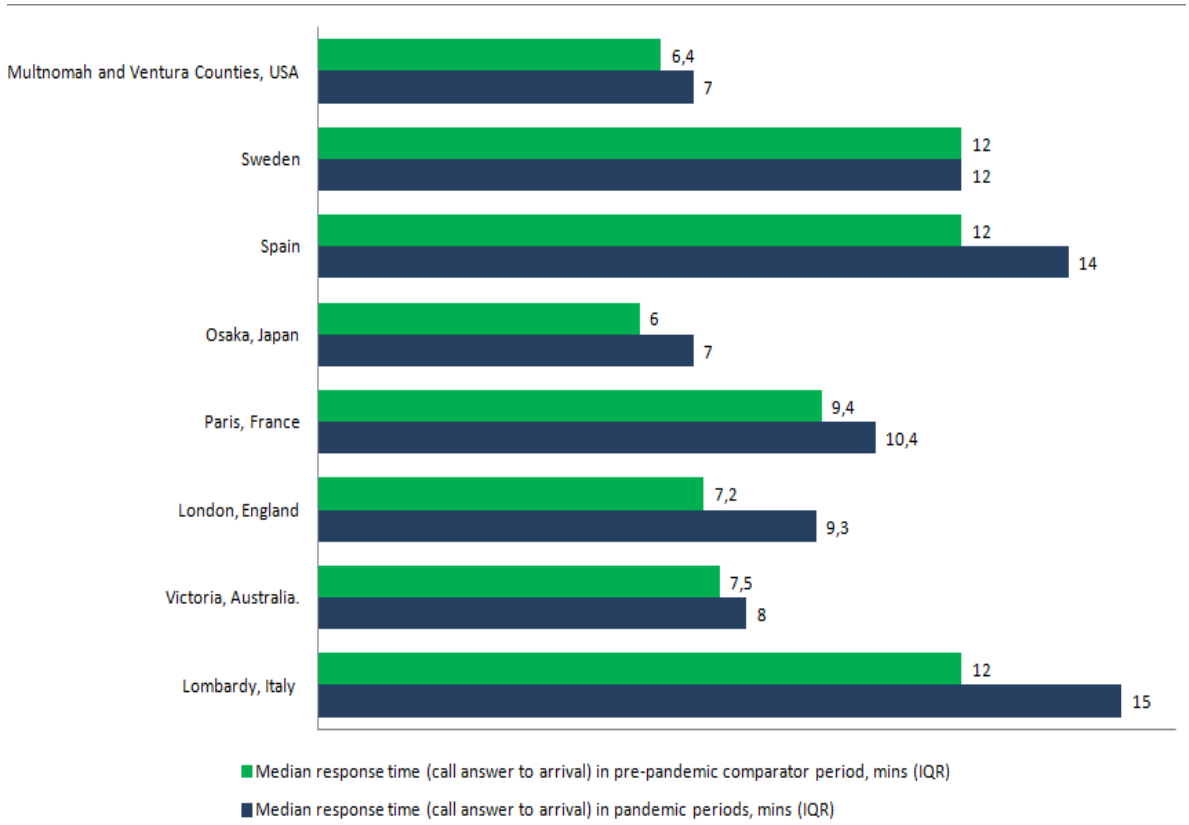


Figure 3. Comparison of the median response time of emergency services (call answer to arrival) between pandemic and pre-pandemic periods. Source: Authors' own work based on items: 8., 9., 10., 11., 12., 13., 14. and 15. of the bibliography

During the COVID-19 pandemic emergency medical teams started CPR less frequently (64,1% versus 69,2% in Italy, 40,6% versus 46,6% in Australia, 36,4% versus 39,6% in England). Time to the first defibrillation and the first administration of epinephrine was delayed. Return of spontaneous circulation was achieved less frequently [Tab. 1].

Table 1. Prehospital ROSC in Lombardy, Victoria, London, Osaka in the pandemic period vs. pre-pandemic period

Region	Prehospital ROSC in pandemic period (%)	Hospital ROSC in pre-pandemic comparator period (%)
Lombardy, Italy	8,6%	**19,8%**
Victoria, Australia	24,0%	**29,6%**
London, England	13,7%	**19,3%**
Osaka, Japan	**9,1%**	**12,5%**

In general, the mortality rate in OHCA increased, even in areas with relatively low COVID-19 incidence (143 cases per 100,000 inhabitants in Multnomah County; 127 cases per 100,000 inhabitants in Ventura County; 159 cases per 100,000 inhabitants in Victoria; 194 cases per 100,000 inhabitants in Paris) [10,12,16].

On the other hand, the OHCA mortality rate in Swiss cantons with the low-incidence rate of COVID-19 (191 cases per 100,000 inhabitants) decreased slightly, showing a divergent trend between overall mortality and OHCA incidence during the COVID-19 pandemic in Switzerland. The reason behind this is not simply to account for the complex pathophysiological factors behind the COVID-19 and its effects on OHCA outcomes but rather points out the multifactorial nature of the issue. Non-biological factors such as healthcare system management, including unsaturated hospital capacity and organization of medical services, especially the fast reorganization of medical services during the onset of the pandemic, have played a significant role in obtaining such results [8].

Termination of resuscitation

The treatment of out-of-hospital cardiac arrest is resource-intensive, with a very small percentage of cases ending with a satisfactory outcome. During a pandemic, resources become severely limited. The general principles of ethics in emergencies and resuscitation remain valid; however, considering the very poor outcome of cardiac arrest in COVID-19 patients and the risk of disease transmission to the rescuers, ERC recommends that healthcare systems implement criteria for decision-making about termination of resuscitation, considering their specific local context [3]. In areas severely affected by the COVID-19 pandemic, such as Detroit in-state Michigan (1666 COVID-19 cases per 100,000 population), modification of

conventional protocols for paramedic management of OHCA should be considered. According to the "distributive justice" principle, emergency medical services must provide "the greatest good for the greatest number of people" by balancing individual patients' needs and the whole community, including prehospital care providers. Being aware of the poor outcome of OHCA, especially during the COVID-19 pandemic, all the more in patients infected with the SARS-COV-2 virus, Leong and colleagues propose significant changes in management in OHCA during the COVID-19 pandemic [4]. They suggest a paradigm shift towards earlier termination of resuscitation (TOR) in patients with asystole as the initial rhythm. Moreover, the authors suggest performing compression-only CPR and communicating with the medical oversight physician to discuss the potential for an early TOR when asystole has been identified.

Michigan was one of the states where the impact of guideline changes on OHCA management was examined. State model protocols included limiting airway interventions to basic life support (BLS) procedures, possible termination of resuscitation after 10 minutes of CPR without ROSC (the previous protocol required 30 min of CPR without ROSC before requesting termination), and transporting to the hospital only those patients in which ROSC lasted more than 5 minutes. Shobi and colleagues compared the management and outcomes of patients with OHCA between 10th March 2020 to 30th April 2020 and 10th March 2019 to 30th April 2019 [21].

Table 2. Termination of resuscitation and ROSC in Michigan in the pandemic period (2020) vs. the pre-pandemic period (2019)

	2020 (n=291)	**2019 (n=180)**	**Odds Ratio or Mean Difference (95% CI)**
Termination of Resuscitation in the Field	69% (200)	36% (64)	**2.36 (1.36–4.07)**
ROSC not obtained	**89% (259)**	**84% (151)**	**1.56 (0.90–2.68)**

The results were not surprising; termination of resuscitation rates nearly doubled in the time of the pandemic. Nevertheless, ROSC rates were similar [Tab. 2].

Conclusions

The COVID-19 pandemic has imposed a significant challenge on emergency medical services, especially while dealing with emergencies such as OHCA.

Based on the research data from all over the world that we have gathered and analyzed, it has had a negative contribution to the OHCA outcomes; both in terms of infection- and pandemic-related issues.

The basic- and advanced life support protocols have been changed and adjusted to the pandemic reality, prioritizing EMS personnel and their safety, especially by implementing PPE. This, in turn, has caused multiple organizational problems such as EMS increased response times, adherence to PPE requirements, PPE shortages, and last but not least - inconveniences in PPE long-term usage experienced by the personnel.

As much as the vast majority of the studies we have analyzed show a positive correlation between the COVID-19 pandemic and the increasing OHCA incidence with poor outcomes, it is essential to point out that the trend was quite the opposite in Switzerland. Thus, good healthcare management and high-quality medical services before the onsetof the pandemic might have contributed to good healthcare management during the pandemicvia optimizing OHCA and resource management while minimizing risk to medical personnel.

References

1. Christian M.D., Couper K.: COVID-19 and the global OHCA crisis: An urgent need for system level solutions. Resuscitation, 2020, 157, 274-276.
2. Baldi E., Sechi G.M., Mare C., Canevari F., Brancaglione A., Primi R., Klersy C., Palo A., Contri E., Ronchi V., Beretta G., Reali F., Parogni P., Facchin F., Rizzi U., Bussi U., Ruggeri S., Visconti L.O., Savastano S., Lombardia CARe researchers: COVID-19 kills at home: the close relation ship between the epidemic and the increase of out-of-hospital cardiac arrests. European Heart Journal, 2020, 41(32), 3045–3054.
3. European Resuscitation Council Covid-19, https://www.erc.edu/covid [cited: 02.05.2021].
4. Leong Y.C., Cheskes S., Drennan I.R., Buick J.E., Lachtmansingh R.G., Verbeek P.R.: Clinical considerations for out-of-hospital cardiac arrest management during COVID-19 J.P. Resuscitation Plus, 2020, 4, 10027.
5. Borkowska M., Smereka J., Safiejko K., Nadolny K, Maslanka M, Filipiak K.J., Jaguszewski M.J., Szarpak L.: Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: a retrospective cohort study. Cardiology Journal, 2021, 28(1), 15-22.
6. Smereka J., Szarpak L.: COVID 19 a challenge for emergency medicine and every

health care professional. American Journal of Emergency Medicine, 2020, 38, 2232–2233.

7. Ruetzler K., Smereka J., Ludwin K., Drozd A., Szarpak L.: Respiratory protection among healthcare workers during cardiopulmonary resuscitation in COVID-19 patients. The American Journal of Emergency Medicine. 2021, 39, 233–234.
8. Baldi E., Auricchio A., Klersy C., Burkart R., Benvenuti C., Vanneta C.H, Bärtschi J.: Out-of-hospital cardiac arrests and mortality in Swiss Cantons with high and low COVID-19 incidence: a nationwide analysis. Resuscitation Plus, 2021, 6, 100105.
9. Baldi E., Sechi G.M., Mare C., Canevari F., Brancaglione A., Primi R., Klersy C., Palo A., Contri E., Ronchi V., Beretta G., Reali F., Parogni P., Facchin F., Bua D., Rizzi U., Bussi U., Ruggeri S., Visconti L.O., Savastano S., Lombardia CARe researchers: Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy. The New England Journal of Medicine, 2020, 30, 383(5), 496-498.
10. Ball J., Nehme Z., Bernard S., Stub D., Stephenson M., Smith K.: Collateral damage: Hidden impact of the COVID-19 pandemic on the out-of-hospital cardiac arrest system-of-care. Resuscitation, 2020, 156,157-163.
11. Fothergill R.T., Smith A.L., Wrigley F., Perkins GD.: Out-of-Hospital Cardiac Arrest in London during the COVID-19 pandemic. Resuscitation Plus, 2021, 5, 100066.
12. Marijon E., Karam N., Jost D., Perrot D., Frattini B., Derkenne C., Sharifzadehgan A., Waldmann V., Beganton F., Narayanan K., Lafont A., Bougouin W., Jouven X.: Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study. The Lancet; PublicHealth, 2020, 5(8), 437-443.
13. Nishiyamaa C., Kiyoharab K., Iwami T., Hayashida S., Kiguchi T., Matsuyama T., Katayama Y., Shimazu T., Kitamura T.: Influence of COVID-19 pandemic on bystander interventions, emergency medical service activities, and patient outcomes in out-of-hospital cardiac arrest in Osaka City, Japan. Resuscitation Plus, 2021, 5, 100088.
14. Ortiz F.R., del Valle P.F., Knox E.C., Fábrega X.J., Navalpotro Pascual J.M., Rodríguez I.M., Azpiazu J.I.R., Vázquez J.A.I., Sucunza A.E., Moreno D.F.A., Canos A.B.F., Blanco M.J.G-O., Cabeza N.L., Gómez B.M., Gómez S.B., Ramas J.A.C., Rozalén M.I.C., Salas F.A.G., Martínez B.F., Codina A.D., OHSCAR investigators: Influence of the Covid-19 pandemic on out-of- hospital cardiac arrest. A Spanish nationwide prospective cohort study. Resuscitation, 2020, 157, 230-240.
15. Sultanian P., Lundgren P., Strömsöe A., Solveig A., Bergström G., Hagberg E.,

Hollenberg J., Lindqvist J., Djärv T., Castelheim A., Thorén A., Hessulf F., Svensson L., Claesson A., Friberg H., Nordberg P., Omerovic E., Rosengren A., Herlitz J., Rawshani A.: Cardiac arrest in COVID-19: characteristicsand outcomes of in- and out-of-hospital cardiac arrest. A report from the Swedish Registry forCardiopulmonary Resuscitation. European Heart Journal, 2021, 42(11), 1094-1106.

16. Uy-Evanado A., Chugh H.S., Sargsyan A., Nakamura K., Mariani R., Hadduck K., Salvucci A., Jui J., Chugh S.S., Reinier K.: Out-of-hospital Cardiac Arrest Responseand Outcomes During the Covid-19 Pandemic. JACC: Clinical Electrophysiology, In Press, Corrected Proof, 2020, 7(1), 6-11.
17. McVaney K.E., Pepe P.E., Maloney L.M., Bronsky E.S., Crowe R.P., Augustine J.J., Gilliam S.O., Asaeda G.H., Eckstein M., Mattu A., Fumagalli R., Aufderheide T.P., Osterholm M.T., Writing group on behalf of the Metropolitan EMS Medical Directors Global Alliance: The relation ship of large city out-of- hospital cardiac arrests and the prevalence of COVID-19. The Lancet, 2021, 34, 100815.
18. Grunau B., Bal J., Scheuermeyer F., Guh D., Dainty K.N., Helmer J., Saini S., Chakrabarti A., Brar N., Sidhu N., Barbic D., Christenson J., Chakrabartia S.: Bystanders are less willing to resuscitate out- of-hospital cardiac arrest victims during the COVID-19 pandemic. Resuscitation Plus, 2020, 4, 100034.
19. Cho J.W., Jung H., Lee M.J. Lee S.H., Lee S.H., Mun Y.H., Chung H-S., Kim Y.H., Kim G.M., Park S.Y., Jeon J.C., Kim C., WinCOVID-19 consortium: Preparedness of personal protective equipment and implementation of new CPR strategies for patients with out-of-hospital cardiac arrest in the COVID-19 era. Resuscitation Plus, 2020, 3, 100015.
20. Borkowska M.J., Jaguszewski M.J., Koda M., Gasecka A., Szarpak A., Gilis-Malinowska N., Safiejko K., Szarpak L., Filipiak K.J., Smereka J.: Impact of Coronavirus Disease 2019 on Out-of-Hospital Cardiac Arrest Survival Rate: A Systematic Review with Meta-Analysis. Journal of Clinical Medicine, 2021, 15, 10(6), 1209.
21. Shobi M., Harrison N., Chalek A.D., Gorelick D., Brennan E., Wise S., Gandolfo L., O'Neil B., Dunne R.: Effects of the COVID-19 pandemic on out-of- hospital cardiac arrest care in Detroit. The American Journal of Emergency Medicine, 2021, 46, 90-96.

Course of COVID-19 - poll among non-hospitalized patients

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Abbreviation list

- COVID-19 - coronavirus disease 2019
- SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2
- COPD - chronic obstructive pulmonary disease
- ARDS - acute respiratory distress syndrome

Introduction

COVID-19 (coronavirus disease 2019) is a disease of which the most common manifestation is an acute respiratory infection caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The first confirmed cases were reported in December 2019 in Wuhan, located in central China [1].

The spread of the virus by airborne droplets, the lack of knowledge about the new pathogen, and traveling without restrictions resulted in reaching pandemic status in March 2020 by the disease caused by SARS-CoV-2. Hundreds of thousands of new cases daily, and the lack of causal treatment became a serious burden on even the most efficient health systems. Due to demographic and economic differences, each country had to develop its plan to protect its citizens. The direction chosen in Poland is, in the first place, the protection of people susceptible to the severe course of SARS-CoV-2 infection. By the severe course of the infection, we mean the need for hospitalization, intensive therapy, respiratory support, and even death. The presence of factors such as senility, lungs and heart problems, obesity, tumors, chronic kidney diseases, type 1 and 2 diabetes, immune deficits, neurological conditions, and strokes are widely recognized as predisposing factors to severe infection [2,3,4]. Current epidemiological data

points out that over 80% of deaths related to COVID-19 are people over the age of 65 [2].

In most cases, the incubation period for COVID-19 ranges from 1 to 14 days [5], while the median is 5.1 [6]. According to calculations, 101 out of 10,000 cases will develop symptoms 14 days after contact with the pathogen [6]. The most common symptoms are fever, dry cough, fatigue. Less common manifestations include loss of smell or taste, shortness of breath, nasal congestion, conjunctivitis, headache, sore throat, nausea, vomiting, diarrhea, confusion, chest pain, chills, muscle and joint pain [4]. According to an analysis conducted by Wu and associates based on data from the Chinese Center for Disease Control and Prevention, 81% of cases are mild, 14% severe, and 5% critical [7].

Aim

The study aimed to compare the course of COVID-19 in the Polish population in various age categories in people with comorbidities and without any burden during the period from March 2020 to April 2021.

Materials and methods

The research group consisted of 271 people of Polish nationality. 13% of the respondents were men, and 87% were women. Most of the respondents were people aged 30-45 - 58%, the second largest group were respondents aged 45-60 years, 16.6% were the youngest (18-29 years old), and 4.4% were people over 60. Thus, 44% of respondents were people diagnosed with at least one chronic disease. Four respondents (1.4%) were vaccinated with a double dose of the COVID-19 vaccine before the disease, twelve (4.4%) were vaccinated with only one dose of the vaccine, and the rest of the study group was unvaccinated. Most of the people (50.9%) participating in the study have a normal BMI, 28.8% are overweight, and the rest (20.3%) are obese. None of the respondents were hospitalized for COVID-19 infection. The survey was conducted online using Google Forms. It consisted of two parts. The first part of the form included: age, gender, education, residence, etc. The second part includes detailed questions about the course of COVID-19 in each of the respondents. The criterion for inclusion in the survey was to have a positive PCR test result. After collecting the answers from the respondents, the results were analyzed and presented in the form of charts.

Results

In this part of the research paper, the results of the survey will be presented. The first question in the second part of the survey concerned the timing of COVID-19 infection. In 2.5% of respondents, the infection occurred in the period from June to September 2020. , 2.2% in the period from March to May 2020. The vast majority - 54% became infected between January and April 2021. The second largest group - 41.3% indicated that the infection lasted between October and December 2020 (Fig. 1).

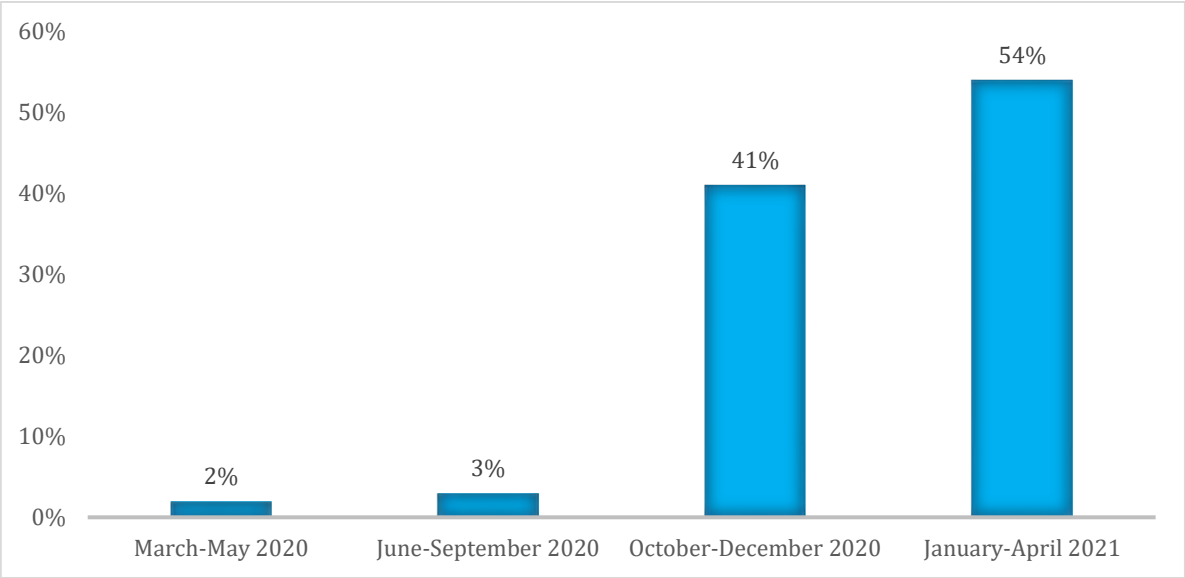


Figure 1. Time of COVID -19 infection among respondents

Another question was about the site of the infection. Chart 2 illustrates the respondents' answers to this question. 27.7 people do not know where the potential infection occurred, 25.3% of the respondents indicated the source of infection at work, 7.4% declared that they got infected from friends, 32% indicated that their household was infected. The other respondents mentioned other places (Fig. 2).

The next question was about the first COVID-19 symptom during an infection. 15.1% of respondents indicated a headache, 16.6% indicated a loss of smell or taste, 16.2% declared that it was weakness, most people - 25.8% chose the answer "cough", 3.7% of respondents indicated that it was a runny nose, 4.8% of the respondents first experienced fever, 3.3% had muscle pain, 2% had diarrhea, and (13.5%) reported dyspnea (Fig. 3).

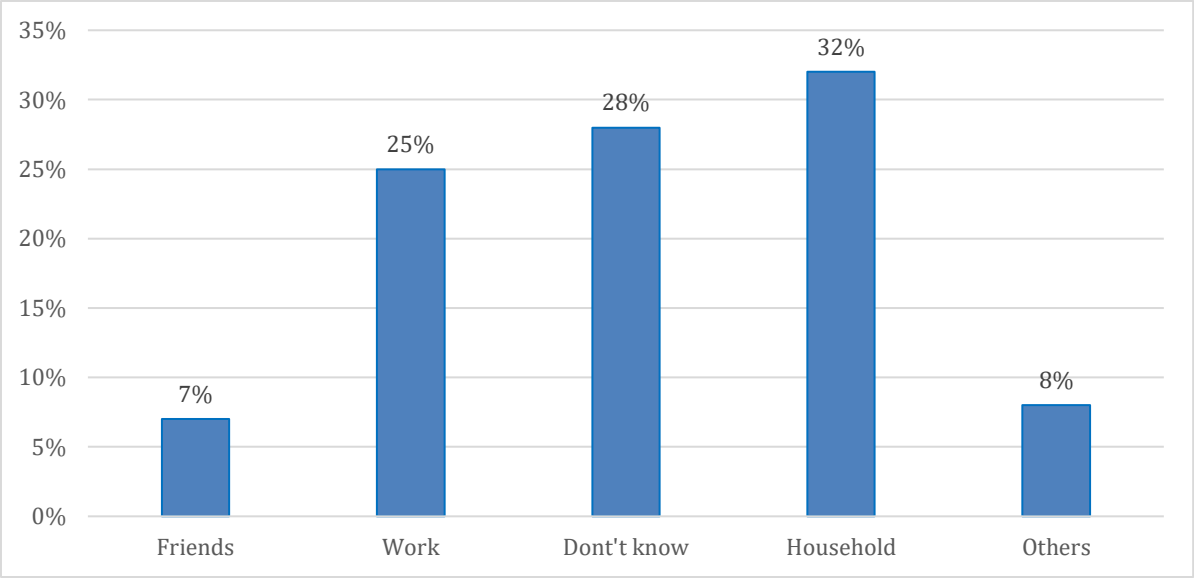


Figure 2.- Place of potential COVID-19 infection in the study group

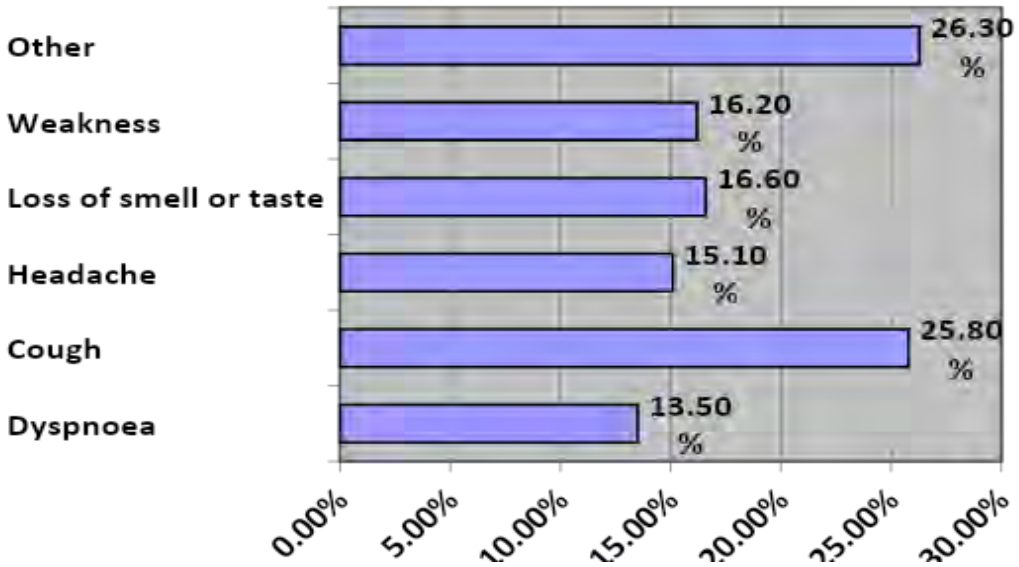


Figure 3.- Responses of respondents about the first symptom observed during COVID-19 infection

The fourth question was about the duration of the symptoms. Most respondents declared that their symptoms lasted from 7 to 14 days (44%). The second most frequently selected answer was the answer "over 21 days" (24%); 59 people (21.7%) indicated that their symptoms lasted 14-21 days, in the remaining (10.3% of respondents), they lasted less than seven days (Fig.4).

Thirty-six respondents who marked the answer with the longest course of the disease - "over 21 days" have been diagnosed with at least one chronic disease. They constitute 55% of

people in this group. However, in the group with the shortest course of the disease, people with comorbidities accounted for only 3.8%.

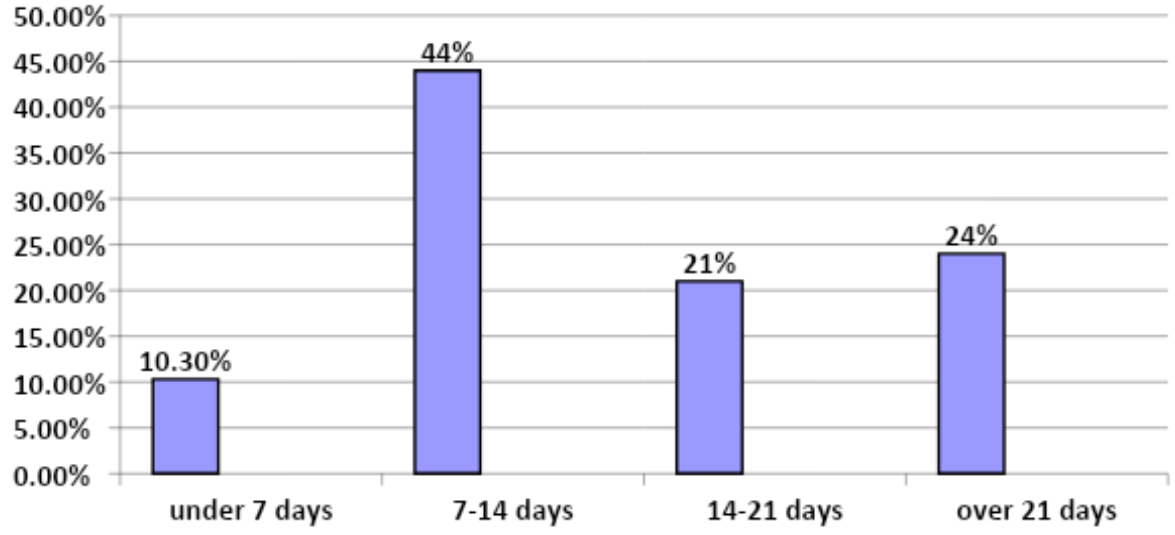


Figure 4. Responses of respondents to the question about the duration of symptoms during COVID-19 infection

The next question concerned the symptom that lasted the longest in the respondents. Most people answered that it was a cough - 19.5%. The second most frequent answer was fatigue (16.6%). In 15.8% of respondents, the longest-lasting symptom was the loss of smell or taste, 9.2% said it was headache or dizziness, 4% indicated runny nose, 4% sinus pain, 4% muscle and joint pain, 2.9 % dyspnoea, 1.8% memory impairment, the least frequent response - 1% was rash and diarrhea - also 1%.

In the next question, the respondents were to choose the course of COVID-19 infection in each of them. Again, there were three responses to choose from: light, medium, or heavy.

Most of them declared that the course of the infection was of moderate severity - 51.2%. 39.9% of respondents described the course of their infection as mild, while the rest (8.9%) declared that they had been severely infected with the SARS-CoV-2 virus.

Among people with a severe course of COVID-19, 54% were overweight or obese, and the rest (46%) had a normal BMI index. In contrast, among people with a mild course of the disease, overweight or obese constituted only 44%, and people with the correct index BMI 56%, respectively.

In addition, people with comorbidities accounted for 66.6% of those with a severe course of infection and only 40.7% of those with a mild course of COVID-19.

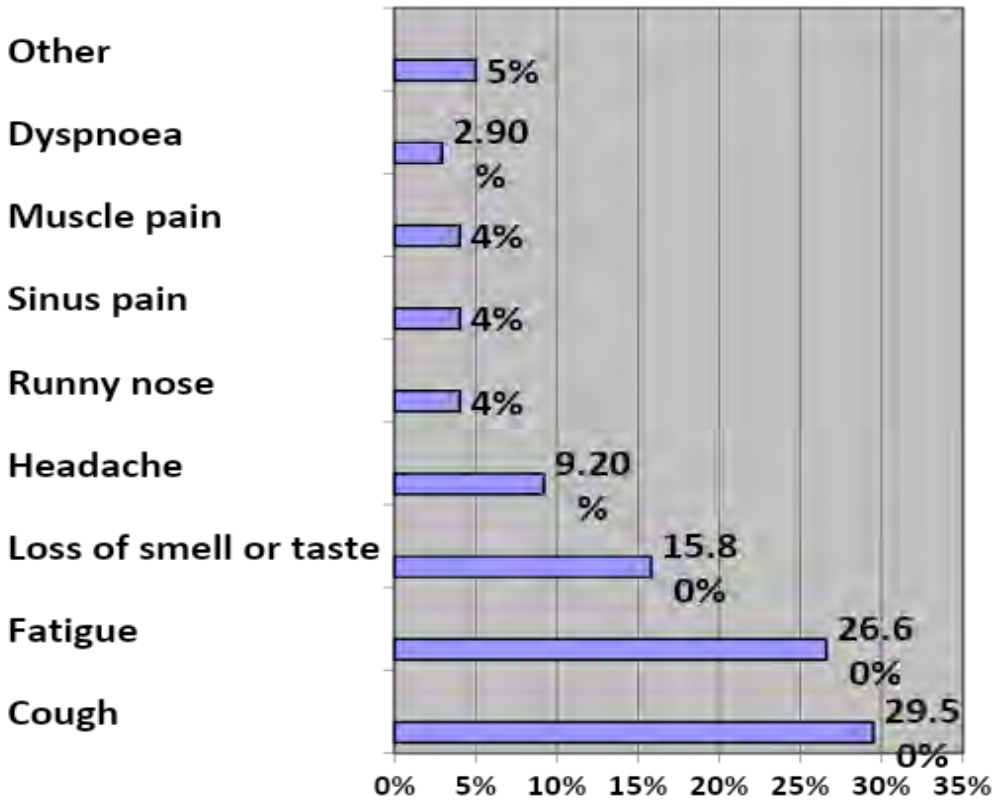


Figure 5. Responses of respondents to the question about the longest-lasting symptom during COVID -19 infection

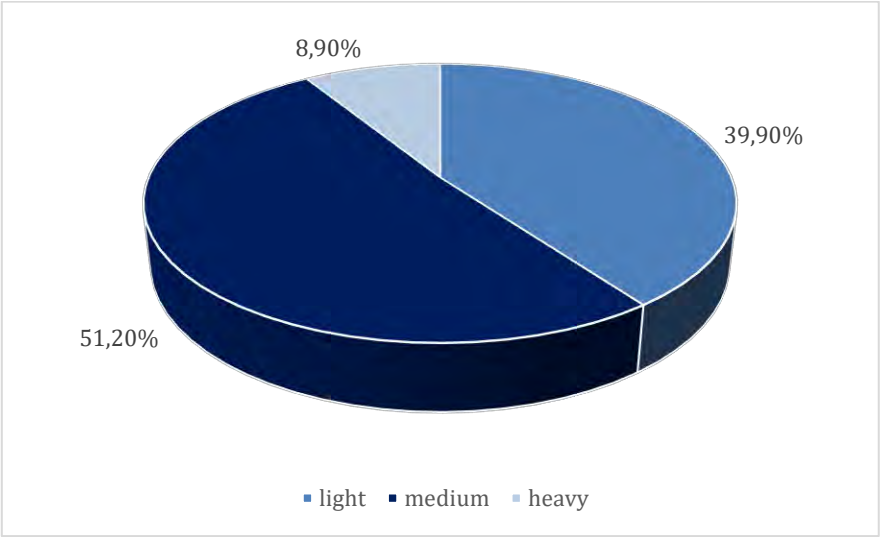


Figure 6. Respondents' answers about the severity of the course of COVID-19 infection in each of them

In the next question, the respondents were asked about the occurrence of complications after the disease. Again, the answers were "Yes" or "No". 24.0% answered in the negative and 76.0% - in the affirmative.

People who answered yes to the previous question we're asked about the type of complications they experienced.

Insomnia occurred in 28.0% of the respondents, chest pain in 19.2%. Chronic fatigue in 50.6% of respondents, exertional dyspnea in 40.2%, problems with concentration in 38.0%, palpitations in 24.4%, memory problems in 32.1%, and persistent olfactory disturbances and / or taste disturbances - in 2.6%.

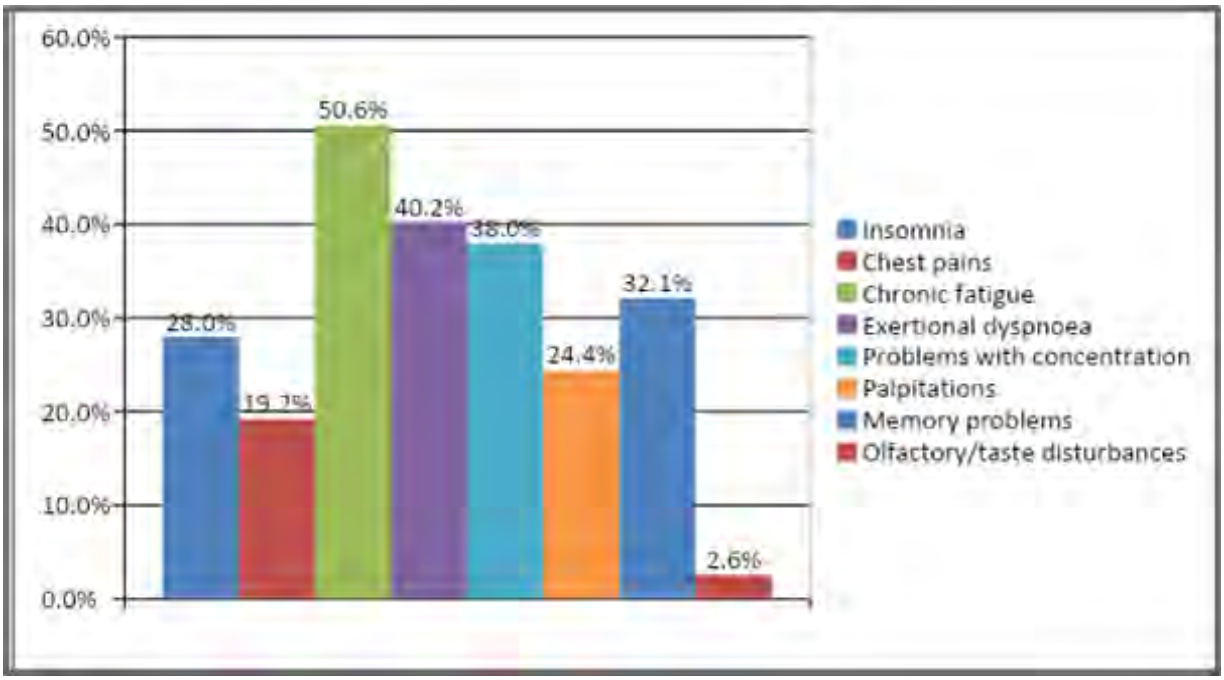


Figure 7. Distribution of the most common complications among people with complicated COVID-19

Among those who developed complications, those diagnosed with a chronic disease in the past were selected. 58.3% of people with complications after COVID-19 had a chronic disease, while 41.7% did not.

In the end, the respondents were asked whether they had returned to full fitness (before falling ill). 36.5% answered in the affirmative and 63.5% - in the negative.

Discussion

In general, the survey results presented above are compatible with expectations based on common knowledge and the global research concerning the course of COVID-19 and biological features of the SARS-CoV-2. The majority of the respondents got infected between

January and April 2021 or between October and December 2020. It can be easily explained, taking into consideration the fact that these are two periods, when the number of cases reported daily was the highest since the outbreak of the coronavirus epidemic in Poland [8].

At that point in time, the virus had spread quickly among the public; therefore, there was a strong possibility of getting infected. Above 30% of participants of this survey claimed that the source of the infection was their household; the second largest group chose the answer "I don't know" and the third believed that it was their workplace. The SARS-CoV-2 routes of transmission, which are via respiratory droplets, contaminated objects, and aerosol, allow the virus to spread easily in poorly ventilated indoor spaces [8]. Numerous studies showed that less than 10% of SARS-CoV-2 infections occurred outdoors [9].

Also, the presymptomatic period and asymptomatic cases, typical for COVID-19, contribute to spreading the infection on both household and work contacts [10].

Although personal protective equipment, disinfection and distance between co-workers are usually introduced to minimize the risk of spreading the virus in the workspace, getting infected is still possible, especially if employees fail to obey protective measures. It can be assumed that a high percentage of people who can not tell where they could have gotten infected comes from high contagiousness of the virus combined with mild or uncharacteristic symptoms in some cases of non-hospitalized patients. Due to the fact that in Poland, most social activities were in some measure limited or even forbidden by government regulations for a significant amount of time, it is not surprising that only 7% of respondents indicate contact with friends as a source of the infection. The next question of the survey raises the issue of initial symptoms of COVID-19. The general distribution of answers, including most common manifestations, proves that there is no specific first sign, even though "cough" was slightly more frequent than the others. The COVID-19, because of its clinical characteristics, requires diagnostic algorithms based on a combination of symptoms, which allow the selection of patients that need to be examined closely in order to prevent further spreading of the virus [11].

The fact that symptoms may occur in multiple combinations and with different intensity in each case has been particularly disturbing and forced health care systems to come up with complex diagnosis plans. Another subject is the duration of the symptoms. Almost a half of participants of this study recovered after 7-14 days, which is typical for a mild to moderate course of coronavirus infection. However, there was also a significant group (24%) of patients that claimed they had presented the symptoms for over 21 days. Over half of these patients have been diagnosed with at least one chronic disease, suggesting that these two facts can be

correlated and that comorbid conditions can prolong the infection. Respondents were also asked about the symptom that remained for the longest time, and most of them indicated that it was either cough or fatigue, which are also two of three the most common manifestations. About 16% chose "loss of smell or taste", which corresponds with prevailing trends. Studies also showed that anosmia and ageusia tend to persist for a longer time in 20-39 [12].

A similar age group (30-45) comprises a big share of participants of this study, so the results match almost perfectly to the mentioned research on the prevalence of smell and taste disorders. Another aspect to the course of COVID-19 infection in our patients was their BMI level. Overweight and obese patients seem to be a rising treatment challenge in modern medicine. Although back in 2009, during the H1N1 influenza outbreak, we learned that severe viral infections are highly related to patients' BMI levels, now the COVID-19 pandemic is making this statement even more unfaltering. Hypertrophic adipocytes are proven to lead to chronic inflammatory states, malfunction of immune system, and interferences with cellular responses, resulting in patients being prone to acute course of SARS-CoV-2 infection [13].

Moreover, obesity is known to be one of the high risk factors of developing diabetes which also is one of the immune system destabilizing factors. Our research results, in terms of COVID-19 course in obese patients, cope with results from other European countries as well as the USA and China [14], proving that over 56% of patients with severe course of COVID-19 infection were overweight or obese while they constituted for only 44% of mild courses. Apart from obesity, there are other comorbidities also affecting the course of infection, such as hypertension (due to upregulated expression of ACE-2 receptors), asthma (impaired secretion of IFN-λ) or COPD (chronic obstructive pulmonary disease) [15].

Comorbidities increase the amount of severe courses of COVID-19 infection and raise chances of lethal ending to it. In our research, patients with coexisting disorders stood for over 66% of cases with severe course of infection. Those patients were also at a bigger risk of developing complications after suffering COVID-19, accounting for over 58% of patients with post-COVID manifestations. Among which most common in tested patients were fatigue (50,6%), exertional dyspnoea (40,2%), and problems with concentration (38%) which corresponds with the presentation in similar patients groups around the world [16].

Although COVID-19 is certainly a new disease entity, post-covid functional limitations are homogeneous to those occurring in other ARDS (acute respiratory distress syndrome) or patients on long-term ICU treatments [17].

Conclusions

The course of infection depends on numerous factors, which influence is either already well recognized or still uncertain and undergoing research. Although scientists around the world continue to investigate the newly discovered coronavirus, it is clear that circumstances such as age, underlying medical conditions, general health state, and the genetic variant of the virus impact the presence and severity of the symptoms.

References

1. Inglot M.: COVID-19. https://www.umed.wroc.pl/sites/default/files/files/aktualnosci/2020/03/COVID_19_1_0_poprawiony_26_03_2020__wersja_po_formatowaniu_(2).pdf (cited 24.07.2021).
2. CDC: People with Certain Medical Conditions. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (cited 24.07.2021).
3. Maragakis L.: Coronavirus and COVID-19: Who is at higher risk? https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/coronavirus-and-covid19-who-is-at-higher-risk (cited 24.07.2021).
4. WHO: Coronavirus disease (COVID-19). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19#:~:text=symptoms (cited 24.07.2021).
5. Europejski Portal Informacji o Szczepieniach: https://vaccination-info.eu/pl/covid-19/fakty-nt-covid-19 (cited 24.07.2021).
6. Lauer S.A., Grantz K.H., Bi Q., Jones F.K., Zheng Q., Meredith H R., Azman A.S., Reich N.G., & Lessler J.: The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Annals of Internal Medicine, 2020, 172(9), 577–582.
7. Wu Z., & McGoogan J.M.: Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA, 2020, 323(13), 1239.
8. Ekram W., Abd El-Wahab., Safaa M. Eassa, Metwally M.: SARS-CoV-2 Transmission Channels: A Review of the Literature. MEDICC Review, 2020, 22(4).
9. Bulfone T.C., Malekinejad M., Rutherford G.W., & Razani N.: Outdoor Transmission

of SARS-CoV-2 and Other Respiratory Viruses: A Systematic Review. The Journal of Infectious Diseases, 2020, 223(4), 550–561.

10. Qiu X., Nergiz A.I., Maraolo A.E., Bogoch I.I., Low N., Cevik M.: The role of asymptomatic and presymptomatic infection in SARS-CoV-2 transmission—a living systematic review. Clinical Microbiology and Infection, 2021, 27(4), 511–519.
11. Tu H., Tu S., Gao S., Shao A., Sheng J.: Current epidemiological and clinical features of COVID-19; a global perspective from China. Journal of Infection, 2020, 81(1), 1–9.
12. Lee Y., Min P., Lee S., & Kim S. W.: Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. Journal of Korean Medical Science, 2020, 35(18).
13. Zhou Y., Chi J., Lv W., Wang Y.: Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev., 2021, 37(2), e3377.
14. Aghili S.M.M., Ebrahimpur M., Arjmand B., Shadman Z., Sani M.P, Qorbani M., Larijani B., Payab M.: Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: a review and meta-analysis. International Journal of Obesity (Lond), 2021, 45(5), 998-1016.
15. Ejaz H,, Alsrhani A,, Zafar A,, Javed H,, Junaid K,, Abdalla A,E,, Abosalif K,O,A,, Ahmed Z,, Younas S.: COVID-19 and comorbidities: Deleterious impact on infected patients. Journal of Infection and Public Health, 2020, 13(12), 1833-1839.
16. Kamal M., Abo Omirah M., Hussein A., Saeed H.: Assessment and characterisation of post-COVID-19 manifestations. International Journal of Clinical Practice, 2021, 75(3), e13746.
17. Lamprecht B.: Gibt es ein Post-COVID-Syndrom? [Is there a post-COVID syndrome?]. Pneumologe (Berl), 2020, 8, 1-4.

Rare adverse events following immunization with mRNA COVID-19 vaccines

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), has afflicted tens of millions of people in a worldwide pandemic. As vaccines are observed to effectively prevent the symptomatic disease and limit its transmission, awareness of actual risks and benefits of immunization is important for managing the pandemic [1].

There are currently (as of July 2021) two mRNA vaccines that have been accepted by the European Medicines Agency (EMA) and the European Commission and which are available for common use in the European Union [2].

The vaccines - Comirnaty (Pfizer-BioNTech) and Spikevax (formerly COVID-19 Vaccine Moderna) - are based on the mRNA technology that has been the research object since the late 1990s. The mRNA vaccines are administered by intramuscular injection and contain nucleoside-modified mRNA (modRNA) particles enclosed in a nano lipid capsule to penetrate the lipid bilayer and enter the host cell [3,4,5]. Modified mRNA particles contain pseudouridine for better translational capacities, increased stability, and no immunogenicity [6]. In addition, these particles encode the SARS-CoV-2 full-length spike protein, modified by two proline mutations that lock the protein in the perfusion conformation [7].

Earlier mRNA vaccine studies have shown that these particles are processed near the injection site, primarily by myocytes, dendritic cells, monocytes, and macrophages, and are drained

to local lymph nodes [8,9].

mRNA vaccines lead to a strong immune response with the production of SARS-CoV-2 spike protein neutralizing immunoglobulins, CD4+ T-cells, CD8+ T-cells, and immune-modulatory cytokines, e.g., type I interferons and interferon-gamma (IFNγ). This harmonized immune response grants the neutralization of free viruses by antibodies and for virus clearance in intracellular compartments by cytotoxic T lymphocytes [10,11,12].

Anaphylaxis

Anaphylaxis is an acute, multisystem, IgE-mediated hypersensitivity reaction that may be potentially lethal [13]. There are several definitions and clinical criteria used to diagnose this condition [14].

The Risk Management Plans submitted by companies to EMA and pharmacovigilance studies are usually based on the Brighton Collaboration Criteria to assess the level of diagnostic certainty for anaphylaxis. The risk of anaphylaxis after vaccinations is generally difficult to estimate due to many adverse events following immunization (AEFIs) being reported as "anaphylaxis" in its broad definition. Apart from observations of actual cases of anaphylaxis after administering the mRNA vaccines, there have been reports of misdiagnosing anaphylaxis as an adverse event following immunization. Certain non-allergic vaccine-related reactions (such as vasovagal reactions and panic attacks which can also induce stridor and dyspnea) may be falsely identified as anaphylaxis due to their similarity to hypersensitivity reactions [15].

The summaries of product characteristics (SmPC) of the mRNA SARS-Cov-2 vaccines listed the frequency of anaphylaxis as "unknown" since no or few anaphylaxis cases were confirmed as an adverse event following the administration of the vaccines during clinical trials and since post-authorization data is still limited [4,5].

According to CDC reports, the frequency of anaphylaxis (which matched the Brighton Collaboration case criteria) after the Comirnaty and Spikevax was estimated to be 11.1 and 2.5 per million vaccine doses, respectively. Furthermore, 86-90% of these cases occurred within the first 30 minutes after dose vaccination, and 81-90% had a history of allergies or allergic reactions [16,17].

As anaphylactic reaction may be life-threatening, close observation of vaccinees for at least 15 minutes following vaccination is recommended to provide adequate treatment, if required [4,5].

Possible vaccine ingredients causing allergic reactions

Both Spikevax and Comirnaty contain polyethylene glycol (PEG), which has been observed to cause allergic reactions [18]. According to a revision of FDA data, PEGs may cause an average of 4 cases of anaphylaxis per year as they are commonly used as an active ingredient in laxatives for bowel preparation, e.g., before colonoscopy procedures [19]. Spikevax also contains tromethamine (THAM), another excipient that may be a potential allergen. THAM is usually used in drugs, contrast agents, and cosmetics [20]. A CDC report on anaphylaxis cases after Spikevax administration has indicated that 2 out of 10 persons who experienced anaphylaxis had a history of hypersensitivity reactions to contrast media [16]. Therefore, the link between anaphylaxis and tromethamine in Spikevax is possible; however, further research is still required to confirm the relationship [20].

Myocarditis

SmPCs for both Spikevax and Comirnaty acknowledge very rare cases of myocarditis and pericarditis observed primarily within 14 days following immunization, more often after the second dose, and more often in younger patients men. However, available data does not indicate the frequency of myocarditis and pericarditis to be higher than in the general population. It is also advised that patients receiving the vaccines should be instructed to seek urgent medical attention if they observe symptoms suggesting myocarditis or pericarditis such as acute and persistent chest pain, shortness of breath or palpitations following immunization [4,5].

A study performed by Montgomery et al. examined 23 patients with identified myocarditis out of 2 810 000 doses of mRNA SARS-CoV-2 vaccines that the U.S. Military Health System administered through April 30, 2021. A total of 23 patients (men, aged 20 to 51) experienced acute chest pain within four days after receiving Comirnaty (7) or Spikevax (13), 20 of whom developed these symptoms following the second vaccination of an appropriately spaced 2-dose series. Twenty-two of the patients, serving in the military at the time, was previously healthy with a high fitness level. Additional testing was performed to rule out other possible factors such as acute COVID-19 and other infections, ischemic injury, or underlying autoimmune conditions. The observed number of identified cases of myocarditis, though the adverse event occurred very rarely,

was said to be higher than expected among male military members after a second vaccination [21].

Acute onset of chest pain four days after vaccination, usually after a second dose, corresponds with findings described in other similar reports and may suggest an immune-mediated mechanism of this adverse reaction [22].

Although the exact mechanism of myocarditis following immunization with mRNA SARS-CoV-2 vaccines is not fully understood, it is important to note that myocardial inflammation is a known complication of COVID-19 infection, occurring in as much as 4,8% of hospitalized patients [23]. Recognizing the efficacy of the SARS-CoV-2 vaccines in preventing infection, any risk of rare adverse events following immunization must be carefully weighed against the very substantial benefit of vaccination [22].

Acute peripheral facial paralysis

Acute peripheral facial paralysis (APFP) is another rare adverse reaction associated mainly with the mRNA SARS-CoV-2 vaccines. During the phase, three clinical trials for Comirnaty and Spikevax, 8 cases of APFP were observed in the participants. In the clinical trial for Comirnaty, there were 4 cases of APFP in the vaccine recipients (out of 18 860 vaccinated) - all described as non-serious. In the clinical trials for the Spikevax vaccine, there were 3 cases of APFP in the vaccine recipients (out of 15 181 vaccinated) and 1 in a placebo recipient (out of 15 170 given placebo). All cases were observed shortly after injection (between 3 and 48 days after the second dose). APFP was resolved in 2 cases and was persisting or being resolved in 6 cases at data cutoff [7,24].

Concerning the mechanism of this reaction, some hypotheses point at the type I interferons that are important for modulating T cell response to mRNA vaccines [11,25]. Transient lymphopenia, observed as an adverse reaction in clinical trials for the mRNA vaccines, is similar to the normal effect of type I interferons [26] and the decreased levels of CD3 and CD4 cells observed during the acute stage of APFP [27]. Moreover, APFP is also reported as an adverse reaction to interferon-α (IFN-α) therapy in hepatitis C virus infection. A possible explanation suggested by Hoare et al. is that interferon-α therapy causes the breakdown of peripheral tolerance to myelin sheath antigens, leading to neuropathy [28]. Though the exact mechanism of association

between facial paralysis and mRNA COVID-19 vaccines remains to be investigated further, the risk for this adverse reaction is presumably very low [25].

Conclusions

Rare adverse events following immunization with mRNA SARS-CoV-2 vaccines reviewed in this paper include anaphylaxis, myocarditis, and acute peripheral facial paralysis. While APFP does not pose a threat to a vaccinee's life, both anaphylaxis and myocarditis may be lethal if not treated properly. Therefore, vigilance against specific symptoms is essential for counteracting dangerous complications. More research is required to fully understand the mechanisms behind such adverse reactions as APFP and myocarditis following immunization with mRNA SARS-CoV-2 vaccines. While analyzing the risks associated with the immunization, it is important to maintain awareness of its efficacy in preventing the symptomatic COVID-19 and limiting its transmission. Severe adverse reactions occur rarely, and the general benefits of immunization outweigh the risk of adverse events.

References

1. Hernández A.F., Calina D., Poulas K., Docea A.O., Tsatsakis M.A.: Safety of COVID-19 vaccines administered in the E.U.: Should we be concerned? Toxicology Reports, 2021, 8, 871-879.
2. European Medicines Agency: COVID-19 vaccines: authorised. [Internet]. c1995-2021 ; Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vacc ines-authorised#authorised-covid-19-vaccines-section [cited 20.07.2021].
3. Bettini E., Locci M.: SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond. Vaccines (Basel), 2021, 9(2), 147.
4. Comirnaty: EPAR - Product information - [Internet]. updated 14.07.2021; Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-infor mation_en.pdf [cited 20.07.2021].
5. Spikevax (previously COVID-19 Vaccine Moderna): EPAR - Product information - [Internet]. updated 14.07.2021; Available from: https://www.ema.europa.eu/en/docu

ments/ product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en. pdf [cited 20.07.2021].

6. Karikó K., Muramatsu H., Welsh F.A.,Ludwig J., Kato H., Akira S., Weissman D.: Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability. Molecular Therapy, 2008, 16(11), 1833-40.
7. Polack F.P., Thomas S.J., Kitchin N., Absalon J., Gurtman A., Lockhart S., Perez J.L., Pérez Marc G., Moreira E.D., Zerbini C., Bailey R., Swanson K.A., Roychoudhury S., Koury K., Li P., Kalina W.V., Cooper D., Frenck Jr R.W., Hammitt L.L., Türeci Ö., Nell H., Schaefer A., Ünal S., Tresnan D.B., Mather S., Dormitzer P.R., Şahin U., Jansen K.U., Gruber W.C.: Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. The New England Journal of Medicine, 2020, 383(27), 2603-2615.
8. Armbruster N., Jasny E., Petsch B.: Advances in RNA Vaccines for Preventive Indications: A Case Study of A Vaccine Against Rabies. Vaccines (Basel), 2019, 7(4), 132.
9. Heine A., Juranek S., Brossart P.: Clinical and immunological effects of mRNA vaccines in malignant diseases. Molecular Cancer, 2021, 20(1), 52.
10. Anderson E.J., Rouphael N.G., Widge A.T., Jackson L.A., Roberts P.C., Makhene M.: Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. The New England Journal of Medicine, 2020, 383(25), 2427-2438.
11. Teijaro J.R., Farber D.L.: COVID-19 vaccines: modes of immune activation and future challenges. Nature Reviews Immunology, 2021, 21(4),195-197.
12. Sahin U., Muik A., Derhovanessian E., Vogler I., Kranz L.M., Vormehr M., Baum A., Pascal K.: COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature, 2020, 586(7830), 594-599.
13. Panesar S.S., Javad S., de Silva D., Nwaru B.I., Hickstein L., Muraro A., Roberts G., Worm M., Bilò M.B., Cardona V., Dubois A.E.J., Dunn Galvin A., Eigenmann P.: The epidemiology of anaphylaxis in Europe: a systematic review. Allergy, 2013, 68(11), 1353-61.
14. Turner P.J., Worm M., Ansotegui I.J., El-Gamal Y., Fernandez Rivas M., Fineman S., Geller M., Gonzalez-Estrada A.: Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organization Journal, 2019, 12(10),100066.

15. Kelso J.M.: Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. Annals of Allergy, Asthma & Immunology, 2021, 127(1), 133-134.
16. CDC COVID-19 Response Team; Food and Drug Administration: Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. Morbidity and Mortality Weekly Report, 2021, 70(4), 125-129.
17. CDC COVID-19 Response Team; Food and Drug Administration: Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine - United States, December 14-23, 2020. Morbidity and Mortality Weekly Report, 2021, 70(2), 46-51.
18. Wenande E., Garvey L.H.: Immediate-type hypersensitivity to polyethylene glycols: a review. Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immuunology, 2016, 46(7), 907-22.
19. Stone Jr C.A., Liu Y., Relling M.V., Krantz M.S., Pratt A.L., Abreo A., Hemler J.A., Phillips E.J.: Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. The Journal of Allergy and Clinical Immunology. In Practice, 2019, 7(5), 1533-1540.
20. Cabanillas B., Novak N.: Allergy to COVID-19 vaccines: A current update. Allergology International, 2021, 70(3), 313-318.
21. Montgomery J., Ryan M., Engler R.: Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the U.S. Military. JAMA Cardiology. Published online June 29, 2021. https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601 [cited 20.07.2021],
22. Shay D.K., Shimabukuro T.T., DeStefano F.: Myocarditis Occurring After Immunization With mRNA-Based COVID-19 Vaccines. JAMA Cardiology. Published online June 29, 2021. https://jamanetwork.com/journals/jamacardiology/fullarticle/2781600 [cited 20.07.2021],
23. Ma K.L., Liu Z.H., Cao C.F., Liu M.K., Liao J., Zou J.B., Kong L.X.: COVID-19 Myocarditis and Severity Factors: An Adult Cohort Study, BMJ Yale, 2020, https://www.medrxiv.org /content/10.1101/2020.03.19.20034124v1.full.pdf. [cited 20.07.2021],

24. Baden L.R., El Sahly H.M., Essink B., Kotloff K., Frey S., Novak R., Diemert D., Spector S.A., Rouphael N., Creech B., McGettigan J., Khetan, S.: Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. The New England Journal of Medicine, 2021, 384(5), 403-416.
25. Soeiro T., Salvo F., Pariente A., Grandvuillemin A., Jonville-Bera A.P.: Type I interferons as the potential mechanism linking mRNA COVID-19 vaccines to Bell's palsy. Therapies, 2021, 76(4), 365–367.
26. Kamphuis E., Junt T., Waibler Z., Forster R., Kalinke U.: Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. Blood, 2006, 108(10), 3253-3261.
27. Greco A., Gallo A., Fusconi M., Marinelli C., Macri G.F., de Vincentiis M.: Bell's palsy and autoimmunity. Autoimmunity Reviews, 2012, 12(2), 323-328.
28. Hoare M., Woodall T., Alexander G.J.: Bell's palsy associated with IFN-alpha and ribavirin therapy for hepatitis C virus infection. Journal of Interferon and Cytokine Research: the official journal of the International Society for Interferon and Cytokine Research, 2005, 25(3), 174-176.

SELECTED PROBLEMS OF MODERN PSYCHIATRY

Psychiatric care in Poland - overview and identification of crucial issues

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Introduction

Efficient and well-organized psychiatric and psychological care is undeniably one of the essential pillars of a healthy and well-functioning society. It is easy to notice the global trend of its reorganization - large and closed care facilities are disappearing in favor of those smaller, more accessible, and closer to the patient. It aims to provide the most comprehensive help possible to the patient. Specialists of all kinds - psychiatrists, psychotherapists - cooperate in centers also in smaller towns, making it much easier for those in need to seek help in difficult life situations and psychiatric care.

Moreover, what does it look like in Poland? Attempts to restructure the entire psychiatric and psychological care system struggle with many problems - from purely systemic and financial to social, related to traditional views of psychiatric patients and, therefore, stigmatization. As a result, the quality of the care provided is low, and unfortunately, only a few seek help in private branches of this sector. The current global situation is the driving force behind changes in this topic. The SARS-CoV-2 virus pandemic seems to be a turning point that has exposed the ubiquitous shortcomings and enormous psychiatric and psychological needs of society. The societal stigmatization of the sick and those seeking help is slowly starting to lose its importance.

The structure of psychiatric care in Poland

At the end of the first half of 2019, in 15 voivodships, there were 40 inpatients, 24-hour

psychiatric wards for children and adolescents. Only Podlaskie Voivodeship has no such institution available. At the same time, 46-day departments operated only in 11 of all the voivodships. No such departments are present in the Opolskie, Lubuskie, Świętokrzyskie, Warmińsko-Mazurskie and Zachodniopomorskie. A total of 171 centers providing psychiatric help operated on an outpatient basis [1].

The best solution for the patient is probably the environment where most of the services are provided in facilities close to his / her place of residence. Such a trend can also be observed - various types of out-of-hospital care are being developed more and more often, enabling the independent functioning of the treated person [2].

For four years now, there has also been a legal ordinance that provides the basis for creating units explicitly designed for this purpose. According to the recommendations contained in the Regulation of the Council of Ministers of February 8, 2017 (Journal of Laws of 2017, item 458), primary psychiatric care is to be provided by the Mental Health Center [3].

Ultimately, one such center is to operate in an area inhabited by no more than 200,000 residents. The Mental Health Center consists of an outpatient team (otherwise known as an outpatient clinic), a community team (highly mobile in principle), a day team, and a hospital team.

The implemented solutions aim to limit the role of round-the-clock hospital care in favor of open and environmental forms. These are modern and effective forms, thanks to which a better patient quality of life is possible [4].

Thanks to introducing the community model of psychiatric health care, people suffering from mental disorders can benefit from assistance close to their residence. This significantly increases its potential availability to patients, and probably also makes it easier to reach more people in need - the stigma of staying in a psychiatric hospital is gone, the patient and his environment have the opportunity to receive an appointment at the clinic similar to a visit to a family doctor. As can be seen, it is essential to develop an effective program, thanks to which departmental facilities with psychiatric departments will be adapted to the conditions of the environmental model of psychiatric care [3].

Financing challenges

Financing psychiatry in Poland has been a huge problem for years. The public expenditure allocated to it from the budget of the National Health Fund is just over

PLN 3 billion. In addition, private expenditure is growing dynamically and currently amounts to approximately PLN 500 million [5]. Regarding psychiatric care spending, Poland is almost at the bottom of the list of European Union countries, which considers the amount of expenditure allocated to public health per capita of a given country. We spend only 3.7% on financing psychiatric care - that is, the previously mentioned less than PLN 3.5 billion - of the entire amount at the disposal of the state health care. This is very low compared to Western European countries, where this percentage is around 6 to 8% [1]. For comparison, in Germany, it is almost four times higher than in Poland [6].

The required percentage postulated based on data from European Union countries, specifying the minimum level of financing psychiatry from public funds is 5%. This means expenses at the level of approximately PLN 4.5 billion per year. Therefore, according to the statistical data, Poland has a chance to achieve the required level of financing for psychiatry no sooner than in the next few years, but only if the private expenditure is taken into account in the amount mentioned above [1].

The Polish psychiatric treatment system is not showing good effectiveness in meeting the needs. It is inefficient; it lacks sufficient resources in many areas, from financial to human resources. Moreover, it is characterized by their unbalanced distribution - mainly the dominance of one-sided, poor offers of large hospital facilities with a significant deficit in community care. Insufficient, irrational financing of psychiatry, discriminating against other areas of health care, is not sufficient for current needs, restoration of resources, or any investments. In addition to the too low total amount allocated from public funds to Polish psychiatry, the structure of these expenses is even more worrying, where as much as 70% is spent on inpatient care and only 1% on community care [7].

The fact that the needs of the psychiatric sector in Poland significantly exceed the resources available is widely known both in the medical community and in the broadly understood public opinion. Therefore, as part of the change in the financial plan, the National Health Fund was to allocate an additional amount of approximately PLN 242 million from the reserve fund. These measures, implemented from April 1, 2020, were intended to support a new model of psychiatric care for children and adolescents [1]. It included launching community care facilities, which were to become the basis of the reformed system of child psychiatry - as the first reference level. The second reference level was mental health centers for children and adolescents, and the third was hospitals.

Expenditure from the National Health Fund budget included in the financial plan for

psychiatric care and addiction treatment for 2020 is PLN 2,756,778. After taking into account the migration reserve, it will amount to PLN 3,153,602 [1]. This means an increase in expenses compared to 2019 at the level of about 9%. However, it should be remembered that although this is undeniable progress, these numbers are still meager compared to Western European standards [8].

It must be noted that the financial situation of psychiatry in Poland is characterized by low expenses for individual health services accompanied by high indirect costs of mental diseases. These indirect costs are mainly related to the absence or incapacity of the employee. In 2012 to 2018, due to various mental disorders, the number of sickness days increased by almost 40%. Additionally, ZUS data shows that sick leave due to mental disorders was longer in 2018 compared to previous years [1]. The above explains an incorrect picture of the relationship, in which the indirect costs of mental disorders exceed the expenses needed for the implementation of health services.

A barrier that significantly hinders the implementation of activities in the field of health promotion - not only mental for the record, however here focusing on the mental aspect - is the shortage of systemic solutions. In particular, this shortage consists of the lack or insufficient amount of funds allocated to the creation or implementation of mental health promotion programs. There is no institution, neither within the structures of the Ministry of Health nor in other ministries, which would be responsible for creating and supervising the state policy in this area. The ministries usually explain their inactivity in this area with difficulties in finding funding [9].

The insufficient financing of psychiatry in Poland results from difficulties with a reimbursed visit to a specialist doctor and social stigmatization of patients in larger psychiatric hospitals, the exceptionally high medicalization of this branch of medicine. This means that numerous medical procedures, especially drugs, are often unnecessarily used, which would not be necessary if the staff was adequately trained and prepared. However, training or learning beyond basic response, such as administering sedatives to the patient and employing highly trained and qualified personnel, is associated with a more significant financial burden.

There is also a problem with how mental health services are financed. It is in the interest of psychiatric hospitals to admit patients for a more extended period of hospitalization. There is a so-called method of person-day payments, from which it follows that "no bed should be idle" – that is, each free place, paid for by the National Health Fund, should be adequately (by filling) managed [6]. This settlement method causes an understandable reluctance of institutions to short hospitalizations of patients, which require more effort from them and would force for

the relationship between patient and institution to be renewed much frequently.

Deficit of psychiatrists

The deficit of psychiatrists in Poland is a significant problem. The need for medical assistance in this area will affect about half of Poles in their life course, and 23.4% of the population can be diagnosed with at least one mental health disorder [1,10]. Unfortunately, the waiting time for a visit to a psychiatrist at the National Health Fund is about four months, and sometimes even longer [10]. With the characteristics of psychiatric diseases, their urgency, and the frequent need for immediate help, it is not easy to consider the length of the queues as optimal.

According to the Supreme Medical Chamber data in Poland, over 4.2 thousand psychiatrists are currently employed - this gives the ratio of approximately nine doctors per 100,000 people. However, there are only about 400 doctors per 7 million young patients [10]. It is also worth noting the uneven distribution of psychiatrists between individual provinces, mentioned earlier in the study [1]. Apart from the insufficient medical staff, the shortages are also visible among nurses, psychologists, and psychotherapists.

One of the first solutions that come to mind, which would help solve many pressing problems, seems to be increasing the number of specialization opportunities for doctors in psychiatry and subsidizing the choice of specialization in psychiatry for both adults and children among medical school graduates. A similar strategy would allow for shortening of the queues to a specialist and would make it possible to 'make up for staff shortages in a relatively short time. It is also important to improve doctors' working environment and develop their cooperation with psychologists, health assistants, and therapists. Working on each of these aspects of patient care can significantly improve the quality of services provided and increase their availability, which should be considered a priority when trying to restructure the entire system.

In order to increase the number of staff, not only doctors should be able to specialize in psychotherapy of children and adolescents - a similar possibility, although more limited, should also be offered to representatives of other medical professions. Since 2018, the pilot program of the mentioned earlier Mental Health Centers has been underway. If this form of assistance proves insufficient, patients will be referred to the Community Mental Health Center.

According to the process, a highly specialized psychiatric care center should be the last place

where a young patient is referred - only if the earlier options are exhausted [10]. Such organization of care allows for faster response and potentially greater effectiveness.

Development of the private sector

Due to the growing needs of patients and health care workers in psychiatric care, the investment activity of private entities in this sector is becoming more and more noticeable [5]. Lack of sufficient funding for the national system pushes both patients and professionals into the private sector. Patients are referred for help outside the system reimbursed by the National Health Fund, usually due to long waiting times for an appointment or the lack of availability of appropriate treatment options. For obvious reasons, not everyone can benefit from a private system. This is because of the high costs of such care, which can be surprisingly high, especially considering the chronic nature of psychiatric diseases and disorders.

Employees, especially psychologists, leave for private establishments due to low wages in the public sector - they look for employment in already existing units or try their hands with their own private business, setting up a company and working on a self-employment basis. Many of them invest on their own in specialist courses required for the psychotherapist. In addition to the costs of specialization, there are also costs related to developing and raising qualifications. This is a large financial investment that public institutions are not able to cover. As a result, experienced psychologists and psychotherapists move away from the state system to private practice. They are guaranteed much higher earnings and development opportunities – normally not available with the national system. All this leads to a situation where the nationally operated system lacks experienced psychologists with specialization and certified therapists. Also, newly hired employees cannot fully replace their predecessors due to insufficient levels of knowledge, skills, and professional experience, which they have no one to learn. The National Health Fund has introduced a scoring system to deal with this shortage of specialists. Here, the services of a clinical psychologist are being equalized to those with only two years of clinical experience, which directly translates into their valuation and thus the financial stability of the units employing them [6].

According to experts from Upper Finance Med Consulting, which had been tasked with analyzing the medical services market in Poland and Europe, "the future of private psychiatric care will be shaped by the constant increase in spending on psychiatric care. The growing scale of patients' needs and the growing tendency to consolidate the sector by private investors" [5].

The agency estimated that the value of the psychiatric sector will increase to PLN 4 billion in 2023, while the growth rate of private expenditure will be even faster [5].

The trend is already clearly visible - there are about 1.5 thousand entities providing services in psychiatric care in Poland, and almost 60% of them are private [5]. Mental health clinics are being opened in almost all private centers. Such services are often offered in parallel and financed by the National Health Fund. Interestingly, Mental Health Centers are an excellent example of the operation of the medical institution without interference from the National Health Fund. At the mental health clinic level, each admission and consultation point must admit every patient who comes to this place and who requires psychiatric help. Psychologists, psychiatric nurses, and community therapists are employed and on duty in such a facility. One admission point can serve the maximum community of 80,000 aged 18 and over [11].

We can distinguish different levels of care provided in a mental health center. These are:

- Mental health clinic with admission and consultation point (outpatient level).
- Psychiatric day ward.
- Community (home) Treatment Teams.
- Psychiatric ward (inpatient, hospital psychiatric services) [11].

The importance of combining the private and public sectors is undeniable - the Allenort Capital Fund has created the most advanced private psychiatric care project in Poland. The Fund allowed for developing a network of institutions and the launching of the first private hospital in Warsaw. ACF is well known for providing comprehensive mental health care [12].

This private hospital provides patients with quick access to medical procedures and ensures the intimacy and comprehensiveness of health care. It is possible to diagnose a patient, treat and treat him/her in one place. All this contributes to a significant shortening of the patient's hospitalization time [12].

Undoubtedly, private investments can strengthen psychiatric care in Poland. With the COVID-19 pandemic at the forefront, increasing challenges are becoming an impulse to invest in the private sector engaged in the field of psychiatry. Therefore, it is necessary to speed up the designating other Centers so that the reformed psychiatric care will be available to all Polish citizens in the next few years. Furthermore, centers responsible for contracting medical care services that currently cover over 90% of our country's inhabitants should undergo a thorough evaluation of procedures, especially in psychiatric care, which would significantly improve their functioning [11].

Suicidology

The suicidal attempt is a serious problem not only for the individual but also for the public healthcare system. There is an easily noticeable relationship - the higher the suicide death rates, the greater the disintegration of society [14]. In Poland, suicides are the seventh cause of death among men and women [15]. Showing one specific cause for suicide is not possible due to its basis stemming from different and co-occurring factors. This is a theatrical interaction effect of the genetic, psychological, sociological, biological, and cultural inputs.

Person deciding to take own life can be characterized by gender, age, residence, education, religion, marital status, or social status. The highest rates of female and male suicide deaths are seen in the age range of 45-60 years; in addition, men commit suicide more frequently than women - in Poland, there is a high disproportion between male and female suicide deaths, amounting to 6: 1. In 2017, the number of deaths due to suicide was 5,276, of which 4,524 were men and only 751 women. Men choose objectively more effective methods of taking their own lives, such as jumping from a height or using firearms. In contrast, women most often use less violent methods for this purpose, e.g., overdosing on sleeping pills. Despite the gender disproportion significantly inclining towards men in successfully taking their own life, women are three times more likely to attempt suicide.

Men use medical help less often and live under the pressure of society related to higher expectations much more often than women, which may impact the reported statistics [14]. According to the World Health Organization, previous attempts were noted in 50% of suicides [16]. Among adolescents, males are five times more likely to commit suicide than females. However, males are three times less likely to attempt suicide [13,17].

The problems that can lead to taking one's own life are different for each age group. However, the basis of such a dramatic decision in young people is most often family problems, breakups, bad financial situations, death of a loved one, conflicts with the law, problems with peers, unwanted pregnancy, and illness [18]. Factors influencing the decision to end life also include the sense of security not being provided by the parents, their alcoholism, broadly understood violence present in the environment, and also the death of the parents [19]. Lack of love, possessiveness, and conflicts between parents also influence suicidal thoughts [20].

There is a correlation between the severity of the suicide incidence among offspring and its upbringing in a dysfunctional family. The school environment also has an impact on the child's development. Teachers should be supportive, adapt the level of teaching, and avoid

treating students impersonally. Children who have learning difficulties commit suicide more often [14]. Rarely is suicide caused by just one reason. Two critical factors are individual suicidal tendencies and a suicidogenic environment, which, when overlapped, may lead to the taking of life [21].

Among adults, their marital status seems to be of significant importance. Widowers, widows, or divorced people are four times more likely to commit suicide than married people. A sudden change in marital status, in particular the first year of being single and alone, is essential in this case. Also noted are socio-professional factors, such as job change or loss, retirement, or dissatisfaction with the current occupation. According to research, the unemployed, manual workers, and farmers most often take their own lives. The problem also applies to people who feel afraid of losing their job and have no prospect of a new source of income. White-collar workers are the least likely to commit suicide. It is likely influenced by an excellent financial situation and high social status.

Another critical factor is a place of living. People living in the city commit suicide less frequently, which may be influenced by greater integration and a stronger family bond, possibly also easier availability of early psychological and psychiatric help.

There is a higher suicide rate in the countryside, which may be related to a greater sense of isolation, loneliness, and difficulty obtaining appropriate help. The most significant number of suicides occurs in the areas with the highest intensity of social and living problems, such as unemployment [14].

The risk of undertaking a suicide attempt is significant in people with labile moods, high levels of manifested aggression and impulsivity, and between people suffering from anxiety [22]. Traumatic events also contribute to the occurrence of pessimistic thoughts. They include addictions, mental illness, imprisonment of a family member, violence, divorce, or separation of parents [23]. The life skills of an individual, which affect the ability to make decisions, solve problems and create relationships with other people, also have a significant impact [24]. Behavioral disorders, including gambling, addiction to electronic devices, sex, work, shopping, may also contribute to suicidal behavior [25].

People living with chronic conditions such as AIDS, cancer, multiple sclerosis, Huntington's disease, and temporal epilepsy are more likely to commit suicide than healthy people. This risk is also greater in people with mental disorders. Most often, it concerns depression, schizophrenia, and bipolar disorder [21]. In the case of biological risk factors of suicide, disturbances in transmission or deficiencies of dopamine and serotonin, which may lead to suicidal thoughts, are essential [26].

Social stigma

Promotion of mental health is often associated with activities undertaken only and exclusively towards people suffering from psychiatric disorders or diseases. This association is caused by insufficient knowledge, not understanding the problem, or reluctance to understand it. The negative overtone of this concept is so deeply rooted in social consciousness that it works on the principle of a cognitive bias in which we equate mental health with mental problems [9]. As a result, most people in Polish society associate mental health with its opposite - disorders, diseases, or any mental problems. This attitude stems from the well-rooted incorrect definition of public health and mental illness [9].

Diagnosing a patient with a mental illness is very often associated with exclusion and a severe social burden. Patients feel fear and anxiety of being perceived only as "a mentally ill person" [27]. The negative perception of mentally ill people leads to a delay in seeking help, diagnosis, and appropriate treatment. These results in a worse prognosis, a lower level of functioning in society, and a deterioration in the patient's quality of life [28]. In colloquial speech, terms describing mentally ill people are used; they are usually offensive and vulgar. All this means that we are dealing with the labeling of patients or people using the help of therapists. Such etiquette violates the psychological comfort and the sense of security and belonging in a given community. These results in the psychiatric patient's perception of the necessity to assume a different role, a kind of change of social identity [27].

The way of thinking about people with mental disorders, incredibly dominant among Poles, is to categorize such patients as a threat requiring isolation from a healthy society. Thus, ever-increasing social isolation is associated with fear of evaluation and rejection but may also increase to psychopathology. Researchers emphasize that mental illness "is not only a set of psychopathological symptoms, but above all the everyday experiences of a mentally ill person, greater dependence on people and institutions, and exclusion from many areas of life" [28].

Diagnosing a mental disorder in our country means stigmatization that patients experience from society, including employers and other aspects of everyday life. An example is when persons diagnosed with a mental illness cannot get married without a court decision [6]. We can read this in art. 12. § 1. "An obstacle to mental illness or mental retardation" contained in the Family and Guardianship Code, according to which "A person who has a mental illness or mental retardation cannot enter marriage. However, if the state of health or mind of such a person does not threaten the marriage or the health of future offspring and if the

person has not been completely incapacitated, the court may allow him/her to marry" [29].

Upon completion of treatment in a psychiatric facility, the Polish state in no way makes it easier for the patient to return to an independent life. There are no initiatives to support these people - those that would help them get an education, find a job, or return to function with family and friends. After leaving the hospital walls, most people become depressed or unable to cope with ordinary activities, thus destroying the chances of living in any social group they are returning to [6].

It is worth paying attention to the stigmatization of patients and psychiatric diseases, which also occurs among representatives of medical professions, including psychiatric care [28].

Indirect contact with the mentally ill healthcare workers experienced embarrassment, compassion, fear, helplessness, and concern [30]. In Nordt's study, psychiatrists used harmful stereotypes when dealing with people suffering from mental disorders more often than the general population. Negative opinions about psychiatric patients, such as being dangerous or unpredictable, were much higher in the group of psychiatrists than in the general population. The author also showed a much higher level of social distancing towards people who have schizophrenia compared to patients with depression and healthy people [31]. It is worth noting that almost 44% of the surveyed psychiatrists (and over 56% of employers) believe that a history of mental illness limits a person's ability to work. As many as 13.5% of Polish psychiatrists (and 30% of employers) claim that a mentally ill person is incapable of teamwork [28].

Stigma and discrimination are the main barriers to the development of psychiatric care. Also, such stigmatization reduces the quality of life of psychiatric patients. Being ashamed of admitting a mental illness and showing a tendency to conceal it are the first steps to perpetuating the stigma process. Stigmatization, in turn, favors the perception that the patient is suffering through the prism of negative stereotypes describing the disease and mentally ill people functioning in society [32].

The concept of promoting mental health requires a positive tone and continued challenge to the stereotypical approach. Therefore, it is essential to disseminate a positive understanding of concepts related to psychology and psychiatry. In order to build a better approach for our society, first of all, it is necessary to educate people - of all ages, social and professional groups - about psychiatric disorders and about building relationships with people suffering from such diseases. Also, the development, funding, and implementation of programs

promoting general acceptance and tolerance of people suffering from psychiatric disorders are of great importance. Furthermore, positive mental health should become the basis of the education program of various professions [9].

Psychiatric care in light of The COVID-19 pandemic

The pandemic changed our world dramatically, influenced the level of stress we felt, and increased our anxiety for our own and loved ones' health. Additionally, isolation led to a greater disintegration of society, and the restriction of movement, set by the governments Resulted in lower overall activity. An isolating person is deprived of appropriate social and physical stimulators, which leads to an increase in the percentage of mental illnesses, including depression. The very process of adapting to this difficult situation is quite stressful and creates a huge psychological burden for many people. Patients who have already been diagnosed with mental illness may experience augmentation of the disease [1]. All this will impact the increase of needs in the field of psychiatric care, all shortly.

In the ongoing pandemic, an increased number of mental disorders manifested as broadly understood panic and anxiety can be seen [33]. This may be related to the mentioned above recommendations for the sanitary-epidemiological regime. In some cases, the new requirements take an exaggerated form, which may be harmful and adversely affect the psyche of those affected. In addition, there is a noticeable tendency in society to pay much more attention to the symptoms of the disease, including coughing and shortness of breath and control body temperature. Before the pandemic, such symptoms, despite their prevalence, did not cause such fears as they do today.

Patients diagnosed with SARS-CoV-2, being quarantined, and their families are exposed to stress and fear for their own and relatives lives. Long-term, chronic stress may result in various types of mental disorders in previously healthy people [33]. An additional aspect is a fear resulting from the ignorance of COVID-19 disease - its course, complications, prognosis, or treatment. The disease entity is something new for us, and we certainly do not know everything about it yet.

In people with primary mental disorders, we observe a limitation of outpatient medical visits in favor of electronic communications, which cannot fully replace the doctor-patient contact [33]. It is also worth noting that the lockdown and limitation of personal medical visits resulted in reducing expenses for the treatment of mental diseases and addictions [1]. In the

meantime, the number of offers of psychological help from hard-to-verify people has increased. Unfortunately, there are no registers to check the qualifications of these people [6].

The current pandemic is a massive challenge for a system based on large institutions. Day psychiatric wards, where patients come to psychotherapeutic sessions and psychiatric help, have been closed due to an epidemic. In contrast, inpatient psychiatric wards only accept the patient inwhere the threat to life and health exists. In addition, planned parties have been suspended [6]. As a result, many patients have lost psychological support.

The mass media provides information about the pandemic, which often shows reality differently and has a huge impact on psychological comfort. This increases the risk of suicidal thoughts and self-destructive behavior. Chaos and lack of guidance will intensify the feeling of threat, fear, incompetence, and helplessness [33]. Therefore, the information provided should be clear and easy to digest. The credibility and wide availability of the media are of great importance in feeling safe and dealing with powerlessness. An improperly delivered health message will never have the desired effect.

Each of the social groups and each individual in a given society is characterized by different mental health needs [33]. Due to the differences among people, information messages should be tailored individually. The implemented systems should take into account different needs.

Particular attention should be paid to health care workers, whose work in a pandemic is associated with occupational risk. The COVID-19 pandemic has exposed significant gaps in health care that affect the quality of working conditions. Due to their exposure to infection, the staff is more susceptible to stress and its effects [33]. Staff shortages in the psychiatric sector and a deficit of personal protective equipment are perceived by employees as an emotional and psychological burden.

The ZUS report shows that in 2020, compared to 2019, there was a significant increase in the number of diagnoses of mental disorders - by as much as 25%. In addition, there was an increase in the number of days of absence due to various types of illness by 37% compared to 2019. The main reasons for the medical leave of absence were depressive episodes, severe stress, adaptation disorders, and anxiety disorders. Not only has there been an increase in the number of dismissals due to mental and behavioral disorders, the average duration of a medical leave of absence has also increased. In 2020, it was a period of up to 19 days [12].

In order to ensure organizational security, specific solutions and procedures should be presented; these should aim at increasing support to the system. It is impossible to achieve a state of mental stability without introducing an executive order.

Conclusions

There is no doubt that Polish psychiatry and psychotherapy began to change slowly along the lines of Western centers. There are new legal solutions that force their restructuring and reorganization. However, one of the biggest problems is a serious issue related to the financing of existing plants and any changes that would have to apply to them. It is necessary to take specific steps that will allow us to increase the expenditure on psychiatric care in Poland. It is also necessary to continue with actions that have already been taken or planned. The problem of financing is significant as it underlies many other weaknesses of the system. It directly influences the deficit of any specialists. Medical specialization is not attractive compared to others - work is low paid, demanding, training conditions are not optimal, and does not encourage specialized competencies development. This problem also applies to psychotherapists, who are worse off with remuneration and where training or development opportunities are not being offered. This leads to highly qualified personnel leaving for the private sector, making it even more difficult to train more professionals to fill the existing public sector gap. There is simply no one to train them. Low funding results in the lack of educational programs that would help society gain familiarization with mental illness and disorders problems. This negatively impacts the perception of people seeking help or receiving psychiatric treatment by their peers living in an intimate environment, which discourages them from continuing treatment or starting it at all. The effect of such an unfavorable combination of many factors is, for example, a high percentage of suicides and suicide attempts.

Increasing the financial expenditure for psychiatric care is only the beginning of the road to repairing its problems. Resources must be managed wisely - further development of small and easily accessible psychiatric and psychological care facilities is necessary, which will make it easier for those in need to seek help. These should also be established at existing facilities, e.g., schools. This would enable for identification of potential problems in adolescents - it would allow, for example, to work with people struggling with various types of addictions, problems in the family environment, or the onset of psychiatric diseases. The pandemic of the SARS-CoV-2 virus has exposed the scale of psychiatric and psychological problems among many societies. It allowed for some taboo topics to be slowly forgotten. More people are indeed treated by a psychiatrist or using psychotherapy to their relatives and colleagues. It is hoped that the current trend will not lose its relevance and will accompany the necessary systemic changes.

References

1. Zdrowie w liczbach: opieka psychiatryczna w Polsce po pandemii. https://www.politykazdrowotna.com/61496,zdrowie-w-liczbach-opieka-psychiatrycz na-w-polsce-po-pandemii?fbclid=IwAR29zCe25xSYMn74bjbCkmxPCZhd-xxaQ2czehM08DSfeeoTD j6TP7lnV1k (data pobrania 30.05.2021).
2. Thornicroft G., Alem A., Dos Santos R.A., Barley E., Drake R.E., Gregorio G., Hanlon C., Ito H., Latimer E., Law A., Mari J., McGeorge P., Padmavati R., Razzouk D., Semrau M., Setoya Y., Thara R. Wondimagegn D.: WPAguidance on steps, obstacles and mistakes to avoid in the implementation of community mental health care. World Psychiatry, 2010, 9(2), 67-77.
3. Rozporządzenie Rady Ministrów z dnia 8 lutego 2017 r. (Dz. U. z 2017 r., poz. 458)
4. The Word Health Report 2001, Mental Health: New Understanding, New Hope. World Health Organization. https://apps.who.int/iris/handle/10665/42390
5. Kazimierska I.: Problem opieki psychiatrycznej w Polsce - analiza rynkowa. https://pulsmedycyny.pl/problem-opieki-psychiatrycznej-w-polsce-analiza-rynkowa-968254 (cited 30.05.2021).
6. Szukalska H.: Stigmatisation and medication: Poland's outdated approach to mental health. https://notesfrompoland.com/2020/05/01/stigmatisation-and-medication-polands-outdated-approach-to-mental-health/ (cited 30.05.2021).
7. Informacja ze spotkania sekcji ochrony zdrowia Narodowej Rady Rozwoju w dniu 9 lutego 2016r. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwj0xIG1ivHwAhWxgP0HHa2ZAyYQFjAAegQIBBAD&url=https%3A%2F%2Fwww.prezydent.pl%2Fdownload%2Fgfx%2Fprezydent%2Fpl%2Fdefaulttaktualnosci%2F5526%2F26%2F1%2Frekomendacje_dot_zdrowia_psychicznego.pdf&usg=AOvVa w1UrTKm-qiALNpvZWIBGbWo (cited 30.05.2021).
8. Okoniewska M.: Coraz większe potrzeby w zakresie opieki psychiatrycznej. https://medycynaprywatna.pl/coraz-wieksze-potrzeby-w-zakresie-opieki-psychiatrycznej-w-polsce/ (cited 30.05.2021).
9. Ochrona zdrowia psychicznego w Polsce: wyzwania, plany, bariery, dobre praktyki. https://www.rpo.gov.pl/sites/default/files/Ochrona_zdrowia_psychicznego.pdf (cited 30. 05.2021).
10. Deficyt psychiatrów, zwłaszcza dziecięcych. https://www.mp.pl/pacjent/psychiatria/aktualnosci/219239,deficyt-psychiatrow-zwlaszcza-dzieciecych?fbclid=IwAR1BATar

cx D0O Uy9k8LYiBJm8iY-t-PAlz6T18mjpR0qleo9wunPRm_HlEk (cited 30.05.2021).

11. Lurka K.: Plan naprawy polskiej psychiatrii. https://www.termedia.pl/mz/Plan-naprawy-polskiej-psychiatrii,41669.html (cited 30.05.2021).
12. Prywatne inwestycje szansą na wzmocnienie opieki psychiatrycznej. https://www. medinwestycje.pl/prywatne-inwestycje-szansa-na-wzmocnienie-opieki-psychiatrycznej- w-polsce (cited 30.05.2021).
13. Światowa Organizacja Zdrowia, Polskie Towarzystwo Suicydologiczne, Biuro Rzecznika Praw Dziecka, Ministerstwo Edukacji Narodowe. (2007). Zapobieganie samobójstwom – poradnik dla nauczycieli i innych pracowników szkoły. Warszawa: Fraszka Edukacyjna.
14. Jarosz M.: Samobójstwo w czasach kryzysu. Suicydologia, 2015a, 5, 5-17.
15. Główny Urząd Statystyczny. Atlas demograficzny Polski. Warszawa 2017
16. Jarosz M.: Samobójstwa, statystyczno–socjologiczna charakterystyka zjawiska. Wybrane zagadnienia patologii społecznej. Wydawnictwa Szkolne i Pedagogiczne, Warszawa, 1975.
17. Kielan A., Olejniczak D.: Czynniki ryzyka oraz konsekwencje zachowań samobójczych z uwzględnieniem problematyki samobójstw dzieci i młodzieży. Dziecko Krzywdzone. Teoria, badania, praktyka, 2018, 17, 3, 9-26
18. Światowa Organizacja Zdrowia, Polskie Towarzystwo Suicydologiczne, Biuro Rzecznika Praw Dziecka, Ministerstwo Edukacji Narodowe. Zapobieganie samobójstwom – poradnik dla nauczycieli i innych pracowników szkoły. Warszawa: Fraszka Edukacyjna, 2007.
19. Uzan G.: Profilaktyka samobójstw. Zdrowie Psychiczne, 1970, 1/2, 120
20. Ringel E.: Gdy życie traci sens. Rozważania o samobójstwie. Wydawnictwo Glob, Szczecin, 1987.
21. Hołyst B.: Suicydologia. Lexis Nexis. Warszawa, 2012.
22. Rosa K., Gmitrowicz A.: Profilaktyczny Program Międzynarodowego Stowarzyszenia Zapobiegania Samobójstwom [in:] Hołyst B. (red.), Suicydologia. Wydawnictwo Naukowe PWN, Warszawa, 2007, 1258-1263
23. Paetzold U.: Zapomniane dzieci. Samobójstwo rodzica i jego wpływ na potomstwo – zadanie dla szkolnej pedagogiki społecznej. Pedagogika Społeczna, 2015, 3(57), 201-215
24. Światowa Organizacja Zdrowia. Life Skills Education. Genewa, 1999.

25. Grant J.E., Potenza M.N., Weinstein A.: Introduction to Behavioral Addictions. The American Journal of Drug and Alcohol Abuse, 2010, 36(5), 233-41
26. Hołyst B.: Interdyscyplinarna problematyka badań etiologii zachowańsuicydalnych. Psychiatria w praktyce ogólnolekarskiej, 2004, 4(3), 130
27. Żaroń A.: Psychiatria środowiskowa z punktu widzenia wybranych potrzeb psychologicznych. Psychiatria, 2018, 15(1), 45–49.
28. Kochański A., Cechnicki A.: The attitudes of Polish psychiatrists toward people suffering from mental illnesses. Psychiatria Polska, 2017, 51(1), 29-44.
29. Art. 12 § 1. Dz.U.2020.1359 t.j., Kodeks rodzinny i opiekuńczy, Przeszkoda choroby psychicznej lub niedorozwoju umysłowego.
30. Dyduch A.: Postawy pracowników opieki zdrowotnej wobec osób chorych na schizofrenię. Rozprawa na stopień doktora nauk medycznych. Medical University of Lublin, Lublin, 2008.
31. Nordt C., Rössler W., Lauber C.: Attitudes of mental health professionals toward people with schizophrenia and major depression. Schizophrenia Bulletin, 2006, 32(4), 709–714.
32. Świtaj P.: Doświadczenie piętna społecznego i dyskryminacji u pacjentów z rozpoznaniem schizofrenii. Institute of Psychiatry and Neurology, Warsaw, 2008.
33. Heitzman J.: Wpływ pandemii COVID-19 na zdrowie psychiczne.Psychiatria Polska, 2020, 54(2), 187-198.

Hallucinogens and placebo: difficulties in establishing a control group in psychedelic studies. Overview of clinical trials with psilocybin

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Abbreviation list

- 5-HT2A - serotonin 2A receptor;
- ASD – Autism Spectrum Disorders;
- DMT – dimetylotryptamine;
- DXM – dextromethorphan;
- METH – d-methamphetamine;
- MDE - 3,4-methylenedioxyethylamphetamine;
- MDMA - 3,4-methylenedioxymethamphetamine;
- LSD – D- lysergic acid diethylamide;
- PCP – phencyclidine;
- PTSD – Post Traumatic Stress Disorder;
- OCD – Obsessive-Compulsive Disorder.

Introduction

Hallucinogens are a diverse group of substances that produce psychological effects by altering a person's awareness and changing perception, thought, and feeling. They are divided into two groups: classic hallucinogens, also known as psychedelics such as LSD (D-lysergic acid diethylamide), psilocybin, peyote, DMT (N,N-dimethyltryptamine), 251-NBOMe and dissociative group, which includes: PCP (phencyclidine), ketamine, DXM (dextrometho-

rphan) and saliva (*Salivia divinorum*) [1]. These psychedelics are a serotonin 2A receptor (5-HT2A) agonist, which anatomically are mostly densely expressed in high-level association cortex [2]. There is also a new "designer drug", 3,4-methylenedioxymethamphetamine (MDMA), which stimulates the release of serotonin and inhibits their reuptake by blocking serotonin transporter [3]. Therefore, as a psychoactive substance, classic hallucinogens can strongly affect the brain, causing the intensified feeling and sensory experiences, panic, paranoia, psychosis, uncoordinated movements, feeling of relaxation and systemic effects: increased heart rate, nausea, loss of appetite, dry mouth and others [3,4].

The effect of psychedelics on different diseases has been analyzed for many years. LSD was used in psychotherapy, especially in the treatment of alcoholism, in the supportive care of the terminally ill cancer patient, among the children with autism spectrum disorders (ASD), [5,6,7,8]. Nowadays, there is more evidence that psychedelics can effectively reduce depression and anxiety symptoms. Moreover, they are well-tolerated and adverse effects like increased heart rate, nausea, loss of appetite, and dry mouth are not common [9]. Additionally, it was observed that after LSD, social inversion and severe personality disturbances improved [10]. LSD and psilocybin also play a role in treating dementia, especially early Alzheimer's Disease (AD) [11]. Activation of 5-HT2A receptors by LSD alters gene expression, which is crucial for schizophrenia. On the animal model of psychosis with low doses of LSD, the process of the development and progression of schizophrenia was analyzed [12,13]. The therapy of LSD in schizophrenic patients had negative consequences like increased depersonalization, perceptual disturbances, and disturbed motor behavior [14]. The positive effect of LSD was observed as a treatment for alcohol use disorder. Her single dose was more beneficial to maintain abstinence compared to naltrexone, acamprosate or disulfiram. The effect of LSD usage was between 6 to 12 months [15].

3,4-Methylenedioxymethamphetamine (MDMA), known as ecstasy (E), was administered to women with chronic Post-traumatic stress disorder (PTSD) from sexual trauma. After the treatment, rating scales measuring the severity of PTSD symptoms showed mean reduction with MDMA, and these effects were sustained to 1-month follow up [16].

Psilocybin, like other psychedelic substances, was shown to decrease symptoms of depression and anxiety, but it was also checked in patients with obsessive-compulsive disorder (OCD) and in smoking cessation [17]. The first study presented that OCD symptoms decreased by 45% without a relationship between the dosage, but the number of patients in this study was only 9 [18]. Patients who wanted to quit smoking were treated with psilocybin during

a 15-week course of cognitive-behavioral therapy. At 6-month follow-up, 12 of 15 subjects demonstrated abstinence and had significantly higher ratings of meaningfulness and spiritual significance [19].

Effects of psychedelics are powerful and vivid, claimed to produce temporary, psychosis-like states [20].

There are various types of the psychedelic experience, including alterations in human consciousness and even mystical-type experiences, such as the feeling of "oceanic boundlessness," internal and external unity, sacredness, and transcendence of time and space [21].

Intense and inimitable sensations accompanying the intake of psychedelic make it virtually impossible to design a clinical trial in which both participants and researchers remain unaware of the outcome of randomization. Consequently, studies concerning such substances face a significant methodological problem, which is proper construction of control groups despite the therapeutic potential. To overcome this problem, researchers attempt to develop a novel study design and placebo.

This work aims to review randomized, double-blind, and placebo-controlled studies of psilocybin, one of the classic serotonergic psychedelics, and analyze each study's control group structure. In this regard, 46 articles were searched via the PubMed database. Eventually, 31 clinical trials were analyzed.

Inactive placebo

In most of the studies patients received inactive placebo, which was lactose [22,23,24,25,26,27,28,29,30], mannitol [31,32], maltose [33], saline [34,35], natrium chloratum 0,9% [36] or just empty capsules [37,38,39,40].

First study conducted by Gouzoulis-Mayfrank et al noted that all (n=8) participants in the psilocybin group and half (n=4) placebo group guessed correctly if they received hallucinogen or placebo [22].

In Smigielski et al. study, the possibility that participants may recognize the active or inactive conditions was considered a major limitation. Researchers choose rather psychedelic naive volunteers and limited opportunity for interpersonal exchange within others [30]. Other researchers did not include their observation in this aspect. However, most of them focused on neuroimaging rather than measuring subjective effects of psilocybin [27,29,32,33,35].

Non-psychoactive substances as placebo - niacin

Considering the above reports of blinding difficulties, some researchers used substances with mild physiological effects as a placebo in control groups. For example, in Grob et al. and Ross et al.'s studies, control groups received 250 mg niacin, which causes little physiological reaction such as flushing and hypotension, sense of warmth, arousal, or tingling sensations without influencing the mental state. However, nearly all participants and therapists guessed correctly whether participants received psilocybin or placebo [17,41].

Psychoactive substances as placebo

In contrast to their first study, Gouzoulis-Mayfrank et al., in the further trial, suggested that design with different psychoactive substances with overlapping psychological effects may be more accurate to maintain blinding procedure. Thus, they randomized participants into four groups; each received psilocybin, 3,4-methylenedioxyethylamphetamine (MDE), and d-methamphetamine (METH) or placebo (empty capsules). Unfortunately, MDE and METH caused notable different effects than psilocybin [37,38,39]. Griffiths et al. used methylphenidate hydrochloride (40 mg/70 kg), a stimulant drug that causes such effects as excitability, nervousness, or positive mood for the control group. After each session, monitors were asked to complete a questionnaire in which they guessed which substance, psilocybin or methylphenidate hydrochloride, was administered. The accuracy of blinding procedures was achieved in 23% of sessions, in which at least one monitor misclassified administered substance [42]. In Barrett et al.'s study, psychoactive drug dextromethorphan was administered as an active comparator condition to psilocybin, next to inactive placebo and low, placebo-like dose of psilocybin. Despite using various methods of blinding, the authors did not include any information if those procedures came out to be successful [43].

Placebo-like psilocybin doses

In many studies, researchers decided to use low or very low doses of psychedelic substances to act as a placebo. In Hasler et al. study, participants received a very low (45 µg/kg), low (115 µg/kg), medium (215 µg/kg), and high (315 µg/kg) dose of psilocybin and lactose as

placebo in random order on five experimental sessions each. Some participants could not guess which dose they had received in which session. Participants could not differentiate between very low and low dose and medium and high dose of psilocybin [44]. The next study, conducted by Griffiths et al., administered 0, 5, 10, 20, and 30 mg/70 kg of psilocybin in ascending or descending sequence. Information about the sequence remained unknown to both participants and monitors. At the end of the study, monitors were asked to complete a questionnaire to assess whether the integrity of blindness procedures had been maintained. Overall, none of the monitors was aware of the order of psilocybin administration [45].

The same survey construction was used in Johnson et al. study. However, no observations were made with regards to the maintenance of the blinding procedures in this study [46].

Griffiths et al. conducted two more studies, in both of which participants received shallow, placebo-like (1 or 3 mg/70 kg) or high (22 or 30 mg/70 kg) doses of psilocybin. As before, after each study, monitors completed questionnaires that asked about the understanding of study design. Most of the monitors guessed the total number of different doses of psilocybin and level of the doses incorrectly, inferences both higher and lower levels than administered in the study. Some monitors believed that a psychoactive drug other than psilocybin or inactive placebo was administered [47,48]. Study conducted by Lewis et al also administered low (0,16 mg/kg) and high (0,215 mg/kg) doses of psilocybin. Both low and high doses displayed a very similar pattern of results in the 5 Dimensions of Altered States of Consciousness scale, statistically differ in the level of audio-visual synesthesiae, elementary imagery, complex imagery, and disembodiment in favor of high dose [49].

Conclusions

The results of so far carried out studies of psychedelics strongly suggest that these substances can be effective therapeutic agents in many various uses. However, a methodological limitation remains: creating a control group that could fulfill the double-blinding integrity, a gold standard of clinical trials nowadays. Maintaining accurate blinding in studies that use such powerful substances as psychedelics appears to be far from easy. To overcome this problem, many researchers try various methods. As an inactive placebo, like disaccharides (lactose, maltose, mannitol), saline, or sodium chloride is very likely to be recognized by both participants and monitors, researchers came up with an idea of using active

substances that could mimic some psychedelics effects. In some trials, niacin was administered as placebo, due to its mild physiological effects. However, it turned out to be too weak to remain unknown. Then psychoactive substances were used, such as MDE, METH, methylphenidate hydrochloride, and dextromethorphan, due to its more or less similar psychological effects to those produced by psychedelic substances. The accuracy of this blinding procedure varied depending on the psychoactive substance. However, the best-measured outcomes appeared in the methylphenidate hydrochloride study. Finally, many studies used very low or low doses of psychedelic substances as a placebo. In those studies, the blinding included both level and sequence of administered doses, which seems to be so far the most efficient method of maintaining the blinding nature of those studies.

References

1. National Institute on Drug Abuse. What are hallucinogens? https://www.drugabuse.gov/publications/drugfacts/hallucinogens (cited: 3.06.2021).
2. Beliveau V., Ganz M., Feng L., Ozenne B., Højgaard L., Fisher P.M., Svarer C., Greve D.N., Knudsen G.M.: A High-Resolution In Vivo Atlas of the Human Brain's Serotonin System. The Journal of Neuroscience, 2017, 4, 37(1), 120-128.
3. Carhart-Harris R.L.: How do psychedelics work? Current Opinion in Psychiatry, 2019, 32(1), 16-2.
4. Nichols D.E.: Psychedelics. Pharmacological Reviews, 2016, 68(2), 264-355.
5. Busch A.K., Johnson W.C.: L.S.D. 25 as an aid in psychotherapy; preliminary report of a new drug. Diseases of Nervous System, 1950, 11(8), 241-3.
6. Pahnke W.N., Kurland A.A., Unger S., Savage C., Grof S.: The experimental use of psychedelic (LSD) psychotherapy. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1971, 4(4), 446-54.
7. Kurland A.A.: LSD in the supportive care of the terminally ill cancer patient. Journal of Psychoactive Drugs, 1985, 7(4), 279-90.
8. Sigafoos J., Green V.A., Edrisinha C., Lancioni G.E.: Flashback to the 1960s: LSD in the treatment of autism. Developmental Neurorehabilitation, 2007, 10(1), 75-81.
9. Muttoni S., Ardissino M., John C.: Classical psychedelics for the treatment of depression and anxiety: A systematic review. Journal of Affective Disorders, 2019, 1, 258, 11-24.

10. Kurland A.A., Unger S., Shaffer J.W., Savage C.: Psychedelic therapy utilizing LSD in the treatment of the alcoholic patient: a preliminary report. The American Journal of Psychiatry, 1967, 123(10), 1202-9.
11. Vann Jones S.A., O'Kelly A.: Psychedelics as a Treatment for Alzheimer's Disease Dementia. Frontiers in Synaptic Neuroscience, 2020, 21, 12, 34.
12. Martin D.A., Marona-Lewicka D., Nichols D.E., Nichols C.D.: Chronic LSD alters gene expression profiles in the mPFC relevant to schizophrenia. Neuropharmacology, 2014, 83, 1-8.
13. Marona-Lewicka D., Nichols C.D., Nichols D.E.: An animal model of schizophrenia based on chronic LSD administration: old idea, new results. Neuropharmacology, 2011, 61(3), 503-12.
14. Itil T.M., Keskiner A., Holden J.M.C.: The use of LSD and ditran in the treatment of therapy resistant schizophrenics (symptom provocation approach). Diseases of Nervous System, 1969, 30, 93–103.
15. Krebs T.S., Johansen P.Ø.: Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. Journal of Psychopharmacology, 2012, 26(7), 994-1002.
16. Bouso J.C., Doblin R., Farré M., Alcázar M.A., Gómez-Jarabo G.: MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. Journal of Psychoactive Drugs, 2008, 40(3), 225-36.
17. Grob C.S., Danforth A.L., Chopra G.S., Hagerty M., McKay C.R., Halberstadt A.L., Greer G.R.: Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of General Psychiatry, 2011, 68(1), 71-8.
18. Moreno F.A., Wiegand C.B., Taitano E.K., Delgado P.L.: Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry, 2006, 67(11), 1735-40.
19. Garcia-Romeu A., Griffiths R.R., Johnson M.W.: Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Current Drug Abuse Reviews, 2014, 7(3), 157-64.
20. Garcia-Romeu A., Richards W.A.: Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. International Review of Psychiatry, 2018, 4, 291-316.
21. Liechti M.E., Dolder P.C., Schmid Y.: Alterations of consciousness and mystical-type

experiences after acute LSD in humans. Psychopharmacology, 2017, 234(9-10), 1499-1510.

22. Gouzoulis-Mayfrank E., Heekeren K., Thelen B., Lindenblatt H., Kovar K.A., Sass H., Geyer M.A.: Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. Behavioural Pharmacology, 1998, 9(7), 561-566.
23. Hasler F., Grimberg U., Benz M.A., Huber T., Vollenweider F.X.: Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. Psychopharmacology, 2004, 172(2), 145-156.
24. Carter O.L., Burr D.C., Pettigrew J.D., Wallis G.M., Hasler F., Vollenweider F.X.: Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. Journal of Cognitive Neuroscience, 2005, 17(10), 1497-1508.
25. Vollenweider F.X., Csomor P.A., Knappe B., Geyer M.A., Quednow B.B.: The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. Neuropsychopharmacology, 2007, 32(9), 1876-1887.
26. Quednow B.B., Kometer M., Geyer M.A., Vollenweider F.X.: Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. Neuropsychopharmacology, 2012, 37(3), 630-640.
27. Bernasconi F., Schmidt A., Pokorny T., Kometer M., Seifritz E., Vollenweider F.X.: Spatiotemporal brain dynamics of emotional face processing modulations induced by the serotonin 1A/2A receptor agonist psilocybin. Cerebral Cortex, 2014, 24(12), 3221-3231.
28. Pokorny T., Preller K.H., Kraehenmann R., Vollenweider F.X.: Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience. European Neuropsychopharmacology, 2016, 26(4), 756-766.
29. Smigielski L., Scheidegger M., Kometer M., Vollenweider F.X.: Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. Neuroimage, 2019, 196, 207-215.
30. Smigielski L., Kometer M., Scheidegger M., Krähenmann R., Huber T., Vollenweider F.X.: Characterization and prediction of acute and sustained response to psychedelic

psilocybin in a mindfulness group retreat. Scientific Reports, 2019, 9(1), 14914.

31. Pokorny T., Preller K.H., Kometer M., Dziobek I., Vollenweider F.X.: Effect of Psilocybin on Empathy and Moral Decision-Making. International Journal of Neuropsychopharmacology, 2017, 20(9), 747-757.
32. Preller K.H., Duerler P., Burt J.B., Ji J.L., Adkinson B., Stämpfli P., Seifritz E., Repovš G., Krystal J.H., Murray J.D., Anticevic A., Vollenweider F.X.: Psilocybin Induces Time-Dependent Changes in Global Functional Connectivity. Biological Psychiatry, 2020, 88(2), 197-207.
33. Preller K.H., Pokorny T., Hock A., Kraehenmann R., Stämpfli P., Seifritz E., Scheidegger M., Vollenweider F.X.: Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. Proceedings of the National Academy of Sciences of the United States of America, 2016, 113(18), 5119-5124.
34. Carhart-Harris R.L., Leech R., Williams T.M., Erritzoe D., Abbasi N., Bargiotas T., Hobden P., Sharp D.J., Evans J., Feilding A., Wise R.G., Nutt D.J.: Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. The British journal of psychiatry: the journal of mental science, 2012, 200(3), 238-244.
35. Petri G., Expert P., Turkheimer F., Carhart-Harris R., Nutt D., Hellyer P.J., Vaccarino F.: Homological scaffolds of brain functional networks. Journal of the Royal Society, Interface, 2014, 11(101), 20140873.
36. Schmidt A., Bachmann R., Kometer M., Csomor P.A., Stephan K.E., Seifritz E., Vollenweider F.X.: Mismatch negativity encoding of prediction errors predicts S-ketamine-induced cognitive impairments. Neuropsychopharmacology, 2012, 37(4), 865-875.
37. Gouzoulis-Mayfrank E., Schreckenberger M., Sabri O., Arning C., Thelen B., Spitzer M., Kovar K.A., Hermle L., Büll U., Sass H.: Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. Neuropsychopharmacology, 1999, 20(6), 565-581.
38. Gouzoulis-Mayfrank E., Thelen B., Habermeyer E., Kunert H.J., Kovar K.A., Lindenblatt H., Hermle L., Spitzer M., Sass H.: Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind

placebo-controlled study. Psychopharmacology, 1999, 142(1), 41-50.

39. Gouzoulis-Mayfrank E., Thelen B., Maier S., Heekeren K., Kovar K.A., Sass H., Spitzer M.: Effects of the hallucinogen psilocybin on covert orienting of visual attention in humans. Neuropsychobiology, 2002, 45(4), 205-212.
40. Pokorny T., Preller K.H., Kraehenmann R., Vollenweider F.X.: Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience. European neuropsychopharmacology, 2016, 26(4), 756-766.
41. Ross S., Bossis A., Guss J., Agin-Liebes G., Malone T., Cohen B., Mennenga S.E., Belser A., Kalliontzi K., Babb J., Su Z., Corby P., Schmidt B.L.: Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of Psychopharmacology, 2016, 30(12), 1165-1180.
42. Griffiths R.R., Richards W.A., McCann U., Jesse R.: Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology, 2006, 187(3), 268-283.
43. Barrett F.S., Carbonaro T.M., Hurwitz E., Johnson M.W., Griffiths R.R.: Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: effects on cognition. Psychopharmacology, 2018, 235(10), 2915-2927.
44. Hasler F., Grimberg U., Benz M.A., Huber T., Vollenweider F.X.: Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. Psychopharmacology, 2004, 172(2), 145-156.
45. Griffiths R.R., Johnson M.W., Richards W.A., Richards B.D., McCann U., Jesse R.: Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology, 2011, 218(4), 649-665.
46. Johnson M.W., Sewell R.A., Griffiths R.R.: Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. Drug and Alcohol Dependence, 2012, 123(1-3), 132-40.
47. Griffiths R.R., Johnson M.W., Carducci M.A., Umbricht A., Richards W.A., Richards B.D., Cosimano M.P., Klinedinst M.A.: Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of Psychopharmacology, 2016, 30(12), 1181-1197.

48. Griffiths R.R., Johnson M.W., Richards W.A., Richards B.D., Jesse R., MacLean K.A., Barrett F.S., Cosimano M.P., Klinedinst M.A.: Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. Journal of Psychopharmacology, 2018, 32(1), 49-69.
49. Lewis C.R., Preller K.H., Kraehenmann R., Michels L., Staempfli P., Vollenweider F.X.: Two dose investigation of the 5-HT-agonist psilocybin on relative and global cerebral blood flow. Neuroimage, 2017, 159, 70-78.

Treatment-resistant depression, a global problem - Ketamine, one of its possible solutions

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Abbreviation list

- SSRIs - selective serotonin reuptake inhibitors
- SNRIs - serotonin norepinephrine reuptake inhibitors
- TCAs - tricyclic antidepressants
- TRD - treatment resistant depression
- rTMS - repetitive transcranial magnetic stimulation
- ECT - electroconvulsive therapy
- tDCS - transcranial direct current stimulation
- NMDA - N-methyl-D-aspartate
- NMDAR - N-methyl-D-aspartate receptor
- PCP - phencyclidine
- HCN - hyperpolarized cyclic nucleotide
- MADRS - Montgomery-Åsberg Depression Rating Scale

Introduction

The objective of this paper is to outline the problem of prevalence of treatment-resistant cases of depression (part 2) and elucidation of ketamine use in their treatment (part 3), as well as evaluation of its efficacy (part 4) and prevalence of side effects that may accompany (part 5.).

For that purpose, literature regarding these subjects was gathered, and results of clinical trials were analyzed.

Treatment-resistant depression

Major depressive disorder is an increasingly frequent health problem. According to the World Health Organisation, it affects at least 264 million people all around the world. Furthermore, depression, if not treated, often leads to suicide, and every year up to 800 000 people die for this reason [1].

The highest incidence of depression is in adults aged 20-40 and is twice more often within women than men. After ischaemic heart disease, it is the second most often cause of disability [2].

Etiopathogenesis of major depressive disorder is really complex. There is a monoamine hypothesis on which the treatment is based. It says that three main neurotransmitters: noradrenaline, dopamine, and serotonin, are responsible for the symptoms of depression. There is a high risk of suffering from depression in people who have family members with mood disorders. A particular set of genes is implicated in the synthesis, degradation, or neurotransmission of serotonin (as well as noradrenaline and dopamine, nevertheless serotonin is the most common cause) and dysfunction in these genes' expression leads to depression symptoms [3].

There is also organic depression, which is caused by systemic diseases such as: dysfunction of an endocrine system, liver or kidney disease, vitamin B_{12} deficiency, or viral infections [4].

Either DSM-5 or ICD-10 criteria (in this classification, major depressive disorder is almost equal to major depressive episode) can be used to diagnose major depressive disorder. According to DSM-5, to diagnose major depressive disorder, a patient needs to show five or more of the particular symptoms during the same two-week period and including at least one of: depressed mood or loss of interest or pleasure. The mentioned symptoms are: depressed mood, loss of interest or pleasure, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation and retardation, fatigue, feeling of worthlessness or excessive or inappropriate guilt, decreased concentration, or recurrent thoughts of death or suicide [5].

The first-choice treatment for depression is selective serotonin reuptake inhibitors (SSRIs). Serotonin-norepinephrine reuptake inhibitors (SNRIs) are dedicated for patients who suffer from a physical pain-related depression. The third main group of antidepressants are tricyclic antidepressants (TCAs), which have the most negative side effects, although sometimes they are the only effective agents in some group of patients. Recently, psychological

therapy is more often recommended as a treatment option. However, metaanalyses show that antidepressant medications are more effective in the treatment of depression than cognitive-behavioral therapy [6].

About 15-30% of patients suffering from major depressive disorder are affected by treatment-resistant depression (TRD). Up to 60% of patients do not respond properly to the two following antidepressant treatments [7]. There is no universally agreed-upon definition of this illness. If the patient doesn't show satisfying response to two or more treatments with agents from two different groups in an adequate duration and dose, he can be considered to suffer from treatment-resistant depression. It is usually said that the duration of the antidepressants' administration should be at least four weeks. After an adequate time, the patient ought to be administered with an agent from an atypical antipsychotic drugs group such as olanzapine or quetiapine [8].

Apart from pharmacotherapy, there are also non-pharmacological methods of treating treatment-resistant depression such as repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), or transcranial direct current stimulation (tDCS). At the current moment, electroshock therapy is more efficient than rTMS. A meta-analysis showed that eight administrations of ECT resulted in remission in 52% of patients, and fifteen administrations of rTMS resulted in remission in 33,6% of patients [9].

Recently, a new agent turned out to positively affect patients suffering from a treatment-resistant depression within hours. This agent is an antagonist of the N-methyl-D-aspartate (NMDA) receptor- Ketamine.

Ketamine - history and mechanism of action

Ketamine is an *N*-methyl-D-aspartate receptor (NMDAR) antagonist. To day, Ketamine is used in medicine as a dissociative anesthetic and analgesic, producing catalepsy, catatonia, and amnesia [10].

Ketamine was first synthesised in 1962 by Calvin L. Stevens. Because there were no severe side effects on animals, the drug was further approved for clinical tests on humans. The first intravenous dose of the drug was medicated on August 3, 1964. The side effects of ketamine use were considered to be rather slight [11].

That provided Ketamine for FDA approval for use in treatment in 1970 [12].

Since then, Ketamine was used by American soldiers in the Vietnam War with great results and minimal side effects. Further studies discovered that diazepam, and currently also midazolam and propofol, are reducing the emergence delirium of Ketamine [13].

Unfortunately, in the course of time, Ketamine showed its shadows. In 1978, Marcia Moore, a yoga teacher, and Howard Alltounian, M.D., a respected clinical anesthesiologist, tried on themselves an influence of Ketamine. It did not take long as they became addicted to the drug and in 1981, frozen skeletal remains of Moore's were found in a forest [14].

Nowadays, Ketamine has its infamy of being a "K drug," providing „new ways of consciousness".

As mentioned above, Ketamine is an NMDAR antagonist. Its anesthetic and analgesic effect takes place mainly due to the process of blocking N-Methyl-D-Aspartate receptors [15] [11].

NMDAR is a glutamate receptor composed of four units encoded by one of the genes: GluN1-3, [11,16], which carries calcium cations (Ca2 +) and few sodium cations (Na +) inside, and potassium cations (K +) outside nerve cells, being responsible for activation of many intracellular processes. In addition to glutamate, it requires the addition of glycine (or serine) for activation. An additional condition for NMDA receptor activation is cell depolarization, which is blocked by the magnesium ion (Mg2 +) at the resting potential [17].

Ketamine acts by non-competitive blocking of the receptor by binding to the allosteric site of phencyclidine (PCP) binding site located inside the canal [18,19,20].

Studies have shown that Ketamine also interacts with other receptors and ion channels, such as dopamine, serotonin, sigma opioid, and cholinergic receptors, and also with hyperpolarized cyclic nucleotide (HCN) - gated channels [20], which may affect its properties as a potential drug in the treatment of depression.

Results of clinical trials - efficacy

Results of studies during which antidepressant properties of ketamine administration, both in single and repeated infusions, in patients suffering from treatment-resistant depression (measured using Montgomery-Åsberg Depression Rating Scale - MADRS and its component regarding suicidal ideation(MADRS-SI) were analysed and collected in the tables below.

Table 1. MADRS scores obtained during studies with a single infusion of 0.5 mg/kg ketamine administered to patients suffering from treatment-resistant depression

Study	Baseline mean MADRS score (SD)	Mean MADRS score after 24h (SD)	ΔMADRS after 24h	Response rate (%)
1[21]	36.9 (5.4)	14.9 (13.1)	-12.0	n/a
2[22]	29.0*(26-34)†	14.5* (2-21)†	-14.5	80.0
3[23]	33.8 (5.8)	6.9 (2.8)	-26.9	90.0
4[24]	34.0 (7.35)	20.3 (n/a)	-13.7	45.8
5[25]	32.6 (6.1)	14.8 (n/a)	-17.8	64.0
6[26]	32.9(9.3)	16.2(10.7)	-16.9	62.1
7[27]	31.8(6.1)	12.9(6.6)**	-18.9	70.8

*Median **Score after 2 hours †Range of values

Table 2. MADRS scores obtained during clinical trials with multiple infusions of 0.5 mg/kg ketamine administered to patients suffering from treatment-resistant depression

Study	Baseline mean MADRS score (S.D.)	Mean MADRS score at the end of the trial (S.D.)	ΔMADRS at the end of the trial	Duration of the trial	Number of infusions	Response rate (%)
1[28]	35.6 (4.8)	9.0 (n/a)	-26.6	13	6	93.3
2[29]	33.3 (4.9)	14.9 (12.0)	-18.4	15	5	68.8
3[29]	35.4 (5.3)	17.7 (7.3)	-17.7	15	7	53.8

Table 3. MADRS-SI results were obtained during clinical trials with a single infusion containing Ketamine at a dose of 0.5 mg/kg when administered to patients suffering from treatment-resistant depression

Study	Baseline mean MADRS-SI score	Mean MADRS-SI score after 24h	ΔMADRS-SI
1[21]	2.9 (1.6)	0.8 (1.4)	2.1
2[22]	2.0* (1-3)†	0.0* (0-2)†	2.0
3[30]	1.6 (1.37)	0.7 (1.1)	0.9
4[31]	3.3 (1.2)	1.6(n/a)***	1.7

*Median ***Score after seven days †Range of values

Results of clinical trials - side effects

Results of studies during which prevalence of adverse effects accompanying the treatment of patients with TRD using Ketamine were analysed and collected in the table below.

Table 4. Occurrence of the treatment-emergent adverse events reported during the clinical trials studying the effects of Ketamine administered either intravenously (1,2) or intranasally (3,4)

Adverse event	Number of a clinical trial			
	1.[22]	**2.[25]**	**3.[32]**	**4.[33]**
Fatigue	20%	15%	29%	28%
Increased heart rate	40%	9%	no data	6%
Somnolence, sedation	60%	15%	25%	no data
Dizziness	30%	45%	67%	17%
Dissociative symptoms	30%	17%	0%	44%
Blurred vision	10%	43%	17%	6%
Nausea	no data	34%	38%	no data
Headache	20%	32%	21%	0%
Anxiety	20%	15%	no data	no data

Discussion

The results of clinical trials, gathered in part 4. show that Ketamine, even after a single intravenous infusion, can provide a significant decrease in MADRS values in patients with Treatment-resistant depression (Table 1).

When MADRS cutoff points are taken into consideration [34], baseline scores of the participants indicated that they are suffering from moderate to severe depression (Table 1 and 2), and after the administration of Ketamine, their results would be interpreted as either mild depression or lack of depressive symptoms.

When suicidal ideation alone was considered (Table 3), mean MADRS-SI scores after

the administration of Ketamine were below 2 - a cutoff point corresponding to the presence of fleeting suicidal thoughts [35]. The results were noticeably better when compared with midazolam in a randomized control trial [30].

Response rates, described as a decrease of baseline MADRS value by 50% or more [25], ranged from 62.1% to 90.0% when single ketamine infusion was administered and between 53.8 and 93.3% when multiple infusions were administered applied. Research results suggest that D-serine and L-serine plasma concentrations may be potential biomarkers of rsponse to ketamine treatment [36]. Concentrations were observed to have lower values in patients responding to treatment with Ketamine than in those who did not show response. Additionally, findings suggest that higher BMI values may correlate with a more significant response to treatment with ketamine [37]. However, the mechanism of such correlation is still unknown. Finally, altered pharmacokinetics of Ketamine, which molecule possesses lipophilic properties, is considered in patients with higher body fat percentages.

The antidepressant effect was apparent rapidly - hours after the infusion [25], and its peak was reached at 24 hours [31] - in contrast to conventional antidepressants, whose effects take place after weeks of daily use [38].

According to analysed studies, median time after the infusion before relapse was between 7 [31] and 15 [22] days after a single infusion and between 18 [27] and 20 [28] days (with singular cases of remaining in the state of remission up to 3 months [23]) after the treatment was ceased when multiple infusions were administered. Thus, despite extending the duration of therapeutic effect by multiple infusions, the relapse inevitably occurs after the discontinuation. In order to maintain that effect, trials using riluzole - a glutamatergic modulator - were conducted, unfortunately with unsatisfying results [39,40].

The authors of the studied clinical trials report that the treatment with Ketamine was associated with minimal adverse events. Most of the symptoms resolved within 4 hours from the beginning of the ketamine administration and were either of a mild or moderate-intensity [33].

The most common treatment-emergent side effects reported by the researchers were dizziness, headache, nausea, numbness, and dissociation, which depended on the dose. Dissociative symptoms did not persist beyond 4 hours after drug administration [41], and were usually resolved within 2 hours [32].

There are reports that the dissociative side effects the participants were experiencing during the infusion of Ketamine correlated with its antidepressant effect [42,43].

In several clinical trials, a mild transient increase in blood pressure was observed. On average, blood pressure values returned to their initial levels soon after the infusion had been finished; however, in one of the studied clinical trials, the infusion of Ketamine was discontinued for two patients due to hemodynamic changes [33,43,44].

A vast majority of the studies report no serious adverse events during the trials. Several studies report no significant deterioration in short-term neurocognitive functions [45].

Regarding drug dependency, there were no reports concerning drug-seeking behaviours during and after the trial [42].

To conclude, available data shows promising results for the application of Ketamine in the therapeutic process of patients suffering from treatment-resistant depression. This may lead to improvement in the quality of life of vast amounts of people in the future, with TRD being a significant problem on a global scale. Although results are still limited and further research may lead to the improvement of knowledge regarding the subject and thus will increase the probability of safe and effective therapy for those in need.

References

1. WHO: Depression https://www.who.int/en/news-room/fact-sheets/detail/depression (cited: 19.07.2021)
2. Gałecki P., Szulc A.: Psychiatria. Wydawnictwo Edra Urban & Partner, Wrocław, 2018.
3. Pasquini M., Berardelli I., Biondi M. Etiopathogenesis of depressive disorders. Clinical Practice & Epidemiology in Mental Health 2014, 10, 166–171.
4. Miyoshi K.: Depression Associated with Physical Illness. Japan Medical Association Journal, 2001, 44(6), 279–282.
5. Substance Abuse and Mental Health Services Administration DSM-5 Changes: Implications for Child Serious Emotional Disturbance, 2016.
6. Boschloo L., Bekhuis E., Weitz E. S.: The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data metaanalysis. World Psychiatry, 2019, 18(2), 183-191.
7. Rush A.J, Trivedi M.H, Wisniewski S.R, et al.: Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. American Journal of Psychiatry, 2006, 163, 1905-1917.

8. Rybicka W.: Jakie leki stosuje się w depresji? https://www.mp.pl/pacjent/psychiatria/choroby/227600,jakie-leki-stosuje-sie-w-depresji (cited: 19.07.2021)
9. Berlim M.T, van den Eynde F., Daskalakis Z.J.: Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and metaanalysis of randomized trials. Depress Anxiety, 2013, 30, 614-623.
10. Duman R.S.: The Dazzling Promise of Ketamine. 2018, https://www.ncbi .nlm.nih. gov/pmc/articles/PMC6353120/ (cited: 24.06.2021)
11. Domino E.F., Warner D.S.: Taming the ketamine tiger. The Journal of the American Society of Anesthesiologists, 2010, 113(3), 678-684.
12. Zanos, P., Moaddel, R., Morris, P. J, Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., Jr, Gould, T. D.: Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacological reviews, 2018, 70(3), 621–660.
13. Fontenot J., Wilson R.D., Domino E.F., Zsigmond E.K., Steen S.N., Aldrete J.A., McDonald J.S., Fox GS.: Efficacy and safety of low-dose intravenous (mini-drip) ketamine hydrochloride and concurrent intravenous diazepam in the induction and maintenance of balanced anesthesia. Clin Pharm Ther, 1982, 31, 225–226.
14. Jansen K.L.: A review of the nonmedical use of Ketamine: Use, users and consequences. J Psychoactive Drugs, 2000, 32, 419–433
15. Franks N.P., Lieb W.R.:Molecular and cellular mechanisms of general anaesthesia. Nature, 1994, 367, 607–614.
16. Vyklicky V., Korinek M., Smejkalova T., Balik A., Krausova B., Kaniakova M., Lichnerova K., Cerny J., Krusek J., Dittert I, et al.: Structure, function, and pharmacology of NMDA receptor channels. Physiological Research, 2014, 63(Suppl 1), S191–S203.
17. Paoletti P., Bellone C., Zhou Q.: NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. Nature Reviews Neuroscience, 2013, 14, 383–400.
18. Kohrs R., Durieux M.E.: Ketamine: teaching an old drug new tricks. Anesthesia & Analgesia, 1998, 87, 1186–1193.
19. Mion G., Villevieille T.: Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neuroscience & Therapeutics, 2013, 19, 370–380.

20. Zanos P., Moaddel R., Morris P.J., Riggs L.M., Highland J.N, Georgiou P., Pereira E.F.R., Albuquerque E.X., Thomas C.J., Zarate C.A., Gould T.D.: Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms Journal of Pharmacology and Experimental Therapeutics, 2018, 70(3), 621-660.
21. Price R.B., Nock M.K., Charney D.S., Mathew S.J.: Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression. Biological Psychiatry, 2009, 66(5), 522–526.
22. Vidal S., Gex-Fabry M., Bancila V., Michalopoulos G., Warrot D., Jermann F., Dayer A., Sterpenich V., Schwartz S., Vutskits L., Khan N., Aubry J-M., and Kosel M.: Efficacy and Safety of a Rapid Intravenous Injection of Ketamine 0.5 mg/kg in Treatment-Resistant Major Depression. Journal of Clinical Psychopharmacology, 2018, 38(6),590-597.
23. Aan het Rot M., Collins K.A., Murrough J.W., Perez A M., Reich D.L., Charney D.S., and Mathew S.J.: Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression. Biological Psychiatry, 2010, 67(2), 139–145.
24. Chen M.-H., Li C.-T., Lin W.-C., Hong C.-J., Tu P. -C., Bai Y. -M., Cheng C. -M., Su T.-P.: Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: A randomized, double-blind control study. Psychiatry Research, 2018, 269, 207–211
25. Murrough J.W., Iosifescu D.V., Chang L.C., Al Jurdi R.K., Green C.M., Perez A.M., Iqbal S., Pillemer S., Foulkes A., Shah A., Charney D. S., Matthew S.J.: Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial. American Journal of Psychiatry, 2013, 170(10), 1134–1142.
26. Correia-Melo F.S., Leal G.C., Vieira F., Jesus-Nunes A.P., Mello R.P., Magnavita G., Caliman-Fontes A.T., Echegaray M.V.F., Bandeira I.D., Silva S.S., Cavalcanti D.E., Araújo-de-Freitas L.S., Luciana M., Tuena Marco A., Nakahira C., Sampaio A. S., Del-Porto J. A., Turecki G., Loo C., Lacerda A. L.T., Quarantini L. C.: Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. Journal of affective disorders, 2020, 1, 264, 527-534.

27. Murrough J.W., Perez A.M., Pillemer S., Stern J., Parides M.K., aan het Rot M., Collins K. A., Mathew S. J., Charney D.S., Iosifescu D.V.: Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression. Biological Psychiatry, 2013, 74(4), 250–256.
28. Albott C.S., Lim K.O., Forbes M.K., Erbes C., Tye S. J., Grabowski J.G., Thuras P., Batres-y-Carr T.M., Wels J., Shiroma P. R.: Efficacy, Safety, and Durability of Repeated Ketamine Infusions for Comorbid Posttraumatic Stress Disorder and Treatment-Resistant Depression. The Journal of Clinical Psychiatry, 2018, 79(3):17m11634.
29. Singh J.B., Fedgchin M., Daly E.J., De Boer, P., Cooper K., Lim P., Pinter C., Murrough J. W., Sanacora G., Shelton R. C., Kurian B., Winkour A., Fava M., Manji H., Van Nueten L.: A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. American Journal of Psychiatry, 2016, 173(8), 816–826.
30. Price R.B., Iosifescu D.V., Murrough J.W., Chang L.C., Al Jurdi R.K., Iqbal S.Z., Soleimani L., Charney D.S., Foulkes A.L., Mathew S. J.: Effects of Ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depression and Anxiety, 2014, 31(4), 335–343.
31. Phillips J.L., Norris S., Talbot J., Hatchard T., Ortiz A., Birmingham M., Owoeye O., Batten L. A., Blier P.: Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. Neuropsychopharmacology, 2019, 45(4), 606-612.
32. Randall L. Morrison, Maggie Fedgchin, Jaskaran Singh, Joop Van Gerven, Rob Zuiker, Kyoung Soo Lim, Peter van der Ark, Ewa Wajs, Liwen Xi, Peter Zannikos and Wayne C. Drevets Effect of intranasal esketamine on cognitive functioning in healthy participants: a randomized, double-blind, placebo-controlled study, Psychopharmacology (Berl), 2018, 235(4), 1107–1119.
33. Kyle A.B. Lapidus, Cara F. Levitch, Andrew M. Perez, Jess W. Brallier, Michael K. Parides, Laili Soleimani, Adriana Feder, Dan V. Iosifescu, Dennis S. Charney and James W. Murrough A.: Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder Biol Psychiatry, 2014, 15, 76(12), 970–976.
34. Herrmann N., Black S.E., Lawrence J., Szekely C., Szalai, J.P.: The Sunnybrook Stroke Study : A Prospective Study of Depressive Symptoms and Functional Outcome. Stroke, 1998, 29(3), 618–624.

35. Montgomery S.: Montgomery and Åsberg (MADRS) Depression Rating Scale https://www.apa.org/depression-guideline/montgomery-asberg-scale.pdf (cited: 28.06. 2021).
36. Moaddel R., Luckenbaugh D.A., Xie Y., Villaseñor A., Brutsche N.E., Machado-Vieira R., Ramamoorthy A., Paz Lorenzo M., Garcia A., Bernier M., Torjman M.C., Barbas C., Zarate C A., Wainer I. W.: D-serine plasma concentration is a potential biomarker of (R,S)-ketamine antidepressant response in subjects with treatment-resistant depression. Psychopharmacology, 2014, 232(2), 399–409.
37. Freeman M P., Hock R.S., Papakostas G.I., Judge H., Cusin C., Mathew S.J., Sanacora G., Iosifescu D.V., DeBattista C., Trivedi M.H., Fava M.: Body Mass Index as a Moderator of Treatment Response to Ketamine for Major Depressive Disorder. Journal of Clinical Psychopharmacology, 2020, 40(3), 287–292.
38. Witkin J.M., Martin A.E., Golani L.K., Xu N.Z., Smith J.L.: Rapid-acting antidepressants. Advances in Pharmacology, 2018, 24(22), 2556-2563.
39. Mathew S.J., Murrough J.W., aan het Rot M., Collins K. A., Reich D. L., Charney, D. S.: Riluzole for relapse prevention following intravenous Ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. International Journal of Neuropsychopharmacology, 2010, 13(1), 71–82.
40. Ibrahim L., DiazGranados N., Franco-Chaves J., Brutsche N., Henter I. D., Kronstein P., Moaddel R., Wainer I., Luckenbaugh D. A., Manji H. K., Zarate C. A.: Course of Improvement in Depressive Symptoms to a Single Intravenous Infusion of Ketamine vs Add-on Riluzole: Results from a 4-Week, Double-Blind, Placebo-Controlled Study. Neuropsychopharmacology, 2012, 37(6), 1526–1533.
41. Jaskaran B. Singh, Maggie Fedgchin, Ella Daly, Liwen Xi, Caroline Melman, Geert De Bruecker, Andre Tadic, Pascal Sienaert, Frank Wiegand, Husseini Manji, Wayne C. Drevets, and Luc Van Nueten.: Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. Biological Psychiatry, 2016, 80(6), 424–431.

LSD - psychedelic renaissance in psychiatry

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Introduction

Psychedelics are substances that alter consciousness via partial agonism to HT-2A receptors and are commonly associated with recreational drug use. In the XX century, they were called "psychotomimetics", then "hallucinogens". Unfortunately, neither of the names described them properly and added a pejorative overtone.
Humphrey Osmond, who came up with the name psychedelics in 1957, wanted to emphasize that they can reveal useful or beneficial properties of the mind [1].

There are three groups of psychedelics: tryptamines (such as psilocin, the metabolite of psilocybin), lysergamides (known especially from the example- LSD), and phenethylamines (such as mescaline, a substance obtained from the cactus) [2]. All of them are agonists of serotonin receptors.

Mood, anger, appetite, attention, and memory are just a few examples of neuropsychological processes modulated by hydroxytryptamine. The effects of the receptor's stimulation depend on a type of modulated receptor [3].

Serotonin binding to postsynaptic HT-2R causes depolarization and excitatory effect [4]. Activation of postsynaptic 5-HT1R leads to hyperpolarization and an opposite effect [3].

Depression, the mental disorder characterised by at least two weeks of depressed mood with loss of interest, decreased appetite and libido, problems with sleeping and concentration, and suicidal thoughts, is one of the most common mental disorders nowadays. Globally, it affects more than 264 million people [5].

It is a brain disorder with pathogenesis hypothetically described as monoamine deficit, neuroendocrinological disturbance, or inflammatory reaction. Medicines, such as SSRI, which increase serotonin by reducing reuptake from the synaptic space, are the commonly taken drugs that help deal with depression, relapse of disorder, or peri-depressive disorders [6,8].

Dayan and Huys described a serotonin model as a substance influencing the way one thought leads to another, proposing that it inhibits chains of negative thoughts. Administration of SSRI leads to early effects, before antidepressant effect, as an evaluation of emotional information seen in healthy patients. It is probably the result of it's mediation via serotonergic innervation to limbic circuitry (e.g. amygdala) [7,8].

Because psychedelics are agonists of serotonin receptors, it is worth thinking about the benefits of using LSD to treat depression and other psychiatric diseases.

Characteristics of the substance

From a biochemical perspective, LSD is an amide of D-lysergic acid and diethylamine and is a derivative of ergoline. LSD can be extracted through a series of chemical reactions. The original reagent obtained from nature are ergot fungus or, infrequently, morning glory seeds, but is also possible to synthesize chemically from simple commercially available sources reagents. LSD is a substance sensitive to changing environmental conditions; therefore it must be stored in a dark place as a saline solution in order not to decompose [11].

Most psychedelics exhibit strong agonism at the serotonin receptors, which results in significant psychomodulatory effects. LSD is distinguished among them by its additional affinity for the D2-receptors. LSD has a high affinity to most serotonin receptor subtypes in the human brain except for the 5-HT3 and 5-HT4. The exact mechanism of action and further biochemical changes of LSD is still undiscovered; however, it is known to increase glutamate levels in the cerebral cortex. Besides, LSD works probably on the principle of positive feedback- it temporarily reduces the level of serotonin, which leads to its overproduction. Some LSD serotonin receptors create specific extracellular loops, which bind this molecule for an extremely long time [14].

Thanks to this, despite the moderate elimination half-life (3 hours) of the substance in the body, its effects persist for a long time (6-12 hours). The pharmacokinetics of the substance has been poorly measured due to the minimal dosage and the achieved concentrations in the body. It is known now that the substance reaches its peak concentration after 1.5 hours and is eliminated according to the first-order kinetics. Only 1% is excreted in the urine unchanged, and the remaining part as metabolites formed with the participation of CYP-450 enzymes, the main of which is 2-oxo-3-hydroxy-LSD (O-H-LSD). The oral bioavailability of the drug is estimated at 70% [15].

The main effects of the drug are perceptual disturbances and hallucinations, as well as alterations in thinking and the sense of self. There may be synesthesia, i.e., sensory perceptions through inappropriate senses, for example, hearing colors or seeing sounds. Vision becomes sharper; edges may vibrate, or, on the contrary, the image blurs, and fractal shapes appear. Users describe their experiences as euphoric, relaxing, and spiritually enlightening. Their mood improves, and they feel better immersed with their surroundings [17].

Most of the physical effects of LSD on the organism are nonspecific and variable. However, common effects are dilation of the pupils, increased sweating, reduced appetite, and insomnia. It also increases blood glucose levels and heart rate. Occasionally, there are goose bumps, jaw clenching, mouth dryness, and hyperreflexia [9,11].

Recreational use of the drug

Due to the necessity to weigh out very small portions of the drug, the substance is most often distributed in the form of small squares of blotter paper soaked in LSD. (similar to small postmarks). In addition, it sometimes comes in the form of small tablets called "microdots", as sugar cubes with droplets of LSD or as the diluted liquid. The recreational dose is approximately 100-200 µg. However, 25 µg is considered as a threshold dose. The price per dose was average between 3 to 8 euros in Poland, as measured in 2013 and 2014 (source https://www.emcdda .europa.eu/data/stats2019/ppp) .

Recreational users experience the adverse effects of LSD from time to time, which they call a "bad trip". These can include panic attacks, severe anxiety, or even psychosis in predisposed individuals. Cases called flashbacks have also been reported where the selective effects of LSD. return over a longer period as short-term episodes. Their regular occurrence appears in the DSM classification under "hallucinogen persisting perception disorder" [16].

Tolerance to LSD has increased with regular consumption and crosses over with other psychedelics such as mescaline or psilocybin. Reduced sensitivity is associated with 5-HT2A-receptor down-regulation [12]. At the same time, LSD is not considered an addictive substance because it does not activate the dopaminergic reward system. In many classifications, LSD has been recognized as a relatively low-harmful psychoactive substance, much less than socially accepted alcohol [13].

Nowadays, it is possible to quantify the concentration of LSD in plasma and urine effectively. This method is sometimes used among hospitalized psychiatric patients,

perpetrators of car accidents, and suicide attempts. Samples should be kept from the sun and refrigerated to the laboratory as soon as possible [10].

History

Swiss chemist Albert Hofmann synthesized lysergic acid diethylamide in Sandoz Laboratories in Switzerland on November 16, 1938. At that time, he was investigating the chemical and pharmacological properties of ergot-fungus affecting rye, which consists of many alkaloids and can also cause ergotism in humans due to the ingestion. His main intention during researching lysergic acid derivatives was to obtain a respiratory and circulatory stimulant. The twenty-fifth substance in the series received an abbreviated name: LSD-25. Animal experiments caused no interest to pharmacologists and physicians; therefore, the substance was set aside. Five years later, as Dr. Hofmann stated, a peculiar presentiment pushed him to repeat the synthesis of LSD-25, which he did on April 16. A small dose incidentally got into the chemist's organism, and during steps of purification and crystallization, he felt the psychedelic effect. After this incident, he surmised a connection between the substance and the effect, so he decided on a self-experiment. Considering the activity of the ergot alkaloids, he took the smallest quantity of lysergic acid diethylamide that could be expected to produce some effect - only 0,25 mg. However, the effect was strong - the doctor felt anxiety, dizziness, and visual distortions. He asked his laboratory assistant to escort him home, so they went on bicycles. Hence the symbol of "Bicycle Day" is well known in the hippie culture. On the way, his condition deteriorated - he underwent a 'bad trip' - he felt even more anxious. People's faces resembled witches or demons, and he was afraid that he might die prematurely. A family doctor examined him at home and detected only highly dilated pupils, so he decided only to observe the course of events. Later the sensations became more positive, and Hofmann even enjoyed hallucinations - both visual and auditory. The next day he was quite tired physically, but his senses were still very sensitive and brought him positive feelings. He decided to send a report to the director of the pharmacological department, Professor Rothlin. His first reaction was incredulous astonishment that such a minor quantity could make a psychoactive effect. Rothlin and his two colleagues repeated the experiment, but with only one-third of the dose. Of course, the effect was still remarkable, and all doubts were gone [18].

In 1949 Dr. Max Rinkel bringing LSD to the USA and gave it to Dr. Robert Hyde, who

took their first acid trip there. They did a survey in 1950 which tested about one hundred volunteers and subsequently reported findings to the American Psychiatric Association. The hypothesis was that this drug could be used in controlled trials of mental disorders and induce temporary model psychosis. Also, an idea was born in scientific circles that alleviating 'the acid' psychosis can bring researchers closer to finding a cure for schizophrenia. However, drug-induced madness was not only a topic for scientists. Beginning in the 1950s, the CIA started to test LSD for potential truth serum and mind-control drug used during interrogations. It was part of a secret project named MK-Ultra, initiated during the early years of the Cold War. Initial reports were very optimistic as they showed that 'the acid' might help reveal information from a subject and cause amnesia afterward. However, next trials pointed out that the drug often causes loss of reality contact and anxiety which eventually made him more of a hindrance than an aid. Some officers even suggested that 'the acid' can be used as a self-administered anti-interrogation substance. Afterall LSD was an aid to interrogations from the mid-1950s through the early 1960s. During those years, a series of experiments on humans were conducted. Some included CIA employees, security officers, and volunteers, but others were carried out on unwitting subjects. Methods applied to this second group violated the Nuremberg Code for medical ethics. As a result, many people died or were traumatized [20,21].

Until 1962, LSD was a little-known drug used on a small scale, mostly scientific. Sandoz Laboratories produced the substance and distributed it legally to psychiatrists and other people who had proper qualifications [19].

In the Canadian province of Saskatchewan psychiatrists Humphry Osmond and Abram Hoffer came with a biochemical theory of schizophrenia, which they elaborated basing on, among other things, LSD experimentation. During the 1950s, they also started a therapy of alcoholism with the use of 'the acid'. The idea was that psychosis induced by the drug was similar to *delirium tremens*, which was at times an onset of achieving sobriety. Their trial from 1953 on two chronic alcoholics was successful - both stopped drinking. Unfortunately, it was a small test sample. Dr. Colin Smith carried out further research on 24 patients, and the effects were also remarkable. In both studies the sense of the therapy was not only giving a high dose of hallucinogenic, but also psychotherapy and environment were significan. After all, their results were criticized by scientists from North America, mostly because of the lack of controlled trials which was becoming an accepted methodology at that time. Finally, in 1962 Dr. Sven Jensen published results of a controlled trial he conducted of treating alcoholism with LSD. 38 of the 58 patients stopped drinking after this 2-year study, but yet soon, psychiatric

treatment with the use of this hallucinogen would be suspended [22]. During the following years, mainly because of the thalidomide-caused worldwide epidemic of deformed babies, LSD was outlawed by many states. Sandoz remarkably reduced their distribution and finally, in 1965, stopped distributing the drug altogether, even though it was not to physicians and researchers [19]. Despite the political situation, many scientists maintained that removing the hallucinogen from the research would deprive psychiatry of the important therapy option [22].

Furthermore, in 1967, "the LSD chromosome scare" began. Dr. Marion Cohen of the State University of New York at Buffalo conducted research in which she observed that LSD damaged white blood cell chromosomes in test tubes. This finding quickly hit the newspapers as people speculated that tragedy would happen again, like the one with thalidomide. Researchers presented contradictory information, and finally, facts overtook the warnings - LSD users gave birth to healthy babies. A study of 120 babies confirmed that [19]. Together with law restrictions, an LSD black market grew. In 1968 government agents reported that the production capacity of seized laboratories was more than 40 million doses per year. Consumption was not estimated well because the production of the rest of the clandestine laboratories was unknown. Nonetheless, it is said that by 1970 somewhere between 1 million and 2 million Americans used 'the acid' [22].

Apart from influencing the work of many artists, like the Beatles, and changing the generation of the 1960s and 1970s who opposed the Vietnam War [23], LSD truly affected the history of psychiatry. It helped to see that mental illnesses are strongly connected with biochemical pathways and boosted the 1950s drug research, which inspired many scientists to develop modern psychopharmaceuticals [22]. According to the words of Dr. John Buckman: "We are now probably ready to return to serious research with LSD. [...] LSD remains one of the most valuable tools in understanding the functioning of the human mind. It mimics, often with great accuracy, the aberrations of mental illness, visionary states, and states of grace" [23].

The legal aspect

The legal and sociological aspects of LSD usage, both the criminalization and the decriminalization of this substance, influences the use in psychiatric treatment of already mentioned mental disorders and recreational use. First and foremost, the law determines what drugs can and cannot be used in medical treatment and thereby directly motivates and prevents both the patient and the physician from using psychedelic drugs in therapy. The legal

perspective also influences the public's attitude towards the usage and possession of LSD. It contributes in particular to the prevention of its use by stigmatizing LSD users as criminals and addicts. An example of a state with strict laws about LSD is Poland, bordering on psychedelics orientated to the Czech Republic. The most important legislation about LSD is called The Act on Counteracting Drug Addiction, dating from 1985 [24]. It was amended recently in 2020. On this basis, Polish law classified LSD and other psychedelics as psychotropic substances from groups I -P. It is the most dangerous psychotropic with no medical use and a high potential for abuse. Adherence to this group also means that substances are excluded from the pharmaceutical market and can only be used for scientific research, usually requiring special permission [25]. The criminal laws indicate a prison sentence of up to 3 years for possession or processing of LSD [26]. In possession of a significant amount of this substance, the penalty may be increased up to 10 years imprisonment [26].

Before the global criminalization, back in the 60's, LSD had been available in the US for over a decade already and had gathered a lot of interest for psychiatric treatment since it showed great results in treating alcoholism in particular, as well as being a potential way to speed up psychological treatment by lowering defenses and providing fast access to the unconscious. Because it was not regulated, it was readily available and became a popular drug in the American counterculture at the time. However, social controversies regarding LSD in those decades led the US government to prohibit it. Production, distribution, usage, and ownership without a special DEA license are forbidden [27]. Shortly after that, in 1971, LSD was banned by the United Nations through the Convention on Psychotropic Substances. This new law affected around 75 states globally; nowadays, the number increased to 185 [28]. Some of these countries, which have had a long history of psychedelic drug usage, such as Peru, also imposed a ban, despite their tradition.

However, as the panic faded, a wave of interest in LSD research and use resurfaced all over the world. As a result, it has become possible to have a certain amount of psychedelics for personal use in some countries such as Portugal or Canada. The public's approach to legalizing LSD is still distrustful, however. Therefore, social initiatives and research organizations such as MIND - European Foundation for Psychedelic Science, MAPS - Multidisciplinary Association for Psychedelic Studies, as well as "psychedelic societies" such as CZEPS in the Czech Republic [29] or Polskie Towarzystwo Psychodeliczne in Poland [30], were founded to convey information about the usage of LSD and similar psychedelic drugs. The main purpose of psychedelic societies is destigmatization of psychedelics, while the scientific organizations

provide resources for scientific research, paving the way for decriminalization. These organizations often collaborate on policy proposals and information for politicians and the general public.

Despite various initiatives to introduce society to the positive effects of LSD, the general public is still not familiar with this topic. This might be confirmed by the number of first-world countries that still have not changed the law on LSD possession and use (also for medical reasons). The unfavorable reputation of using psychedelics in the last century, to this day, also arouses aversion in the public space. It prejudices the interests of professional use of LSD in medicine and limits medical research on that subject. From the point of view of treating mental disorders with psychedelics - lack of availability to professional treatment prevents help or forces patients to use LSD and other psychedelics on their own. This kind of situation places sufferers in a dilemma between fighting for recovery or committing a criminal offense.

There is, however, also a good reason for criminalization, as the use of large doses of LSD has been associated with psychosis and the onset of schizophrenia. Yet, this risk seems directly linked to a predisposition for this type of mental disorder. In modern-day research, this risk is mitigated by screening for psychosis in the research participant and his or her family history. For decriminalization to happen, however, there needs to be more research in the safety and clinical utility of the drug to convince both politicians and the public that this is a good idea. Many psychiatrists are also opposed to using an experimental drug known to cause harm to some patients before sufficient evidence is gathered that it is, in fact, both better and safer than current methods. The number of scientific studies on the use of psychedelic drugs both in treatment and recreationally is currently higher than ever in the '60s, however. As a result, there is momentum for decriminalization and destigmatization like never before. As one of the few associations in the world – Czech National Institute of Mental Health in coordination with Charles University in Prague - carries out valuable and professional research on LSD, which enables the dissemination of reliable information about this substance, shrouded in many mystical stories [31].

Large amounts of research is also conducted in the US and UK on the therapeutic use of drugs like psilocybin from mushrooms and MDMA, and ketamine, potentially paving the way for the destigmatization of psychedelic drugs in general. The duration of the LSD experience lasts much longer than psilocybin which provides a similar effect, and as a result, LSD isn't a primary candidate for therapeutic use. As a result, there is still a long way to go for the decriminalisation of its use.

Neuroplasticity and neuritogenesis promotion of LSD and its potential use in treating neuroathropic diseases

Psychiatric diseases such as depression are known to cause atrophy of brain cells, especially in the prefrontal cortex. Unfortunately, there are still no drugs sufficient enough to reverse these effects. Recent studies on psychedelics and ergolines (lysergic acid diethylamide [LSD]) have shown promising results. However, the question of whether those substances are a valuable tool in treating neurotropic diseases is still unanswered.

LSD has proven effective in promoting spinogenesis and synaptogenesis in rats and Drosophila species (in vivo) and in rodent cortical cultures (in vitro). It has increased the dendritic spine density but did not alter the number of neurons or the cell size or length of the longest axon.

The study shows its high affinity causes the neuroplasticity and neuritogenesis effect of LSD to the 5-HT2A receptor, which affects TrkB and then activates mTOR pathway similarly to the BDNF protein [32].

Another study shows the ability of LSD to increase the BDNF blood plasma levels in healthy volunteers in acute administration of the substance [33].

The Brain-derived neurotrophic factor (BDNF) is a molecule that affects differentiation, maturation and survival of neurons through its high affinity to tropomyosin receptor kinase B (TrkB) and its secondary messengers (which later affects the CREB protein, thus regulating the expression of genes). BDNF serum levels were lower in patients with schizophrenia. BDNF might have a role in the pathophysiology of DM2 and depression [34].

All of the above show the potential of LSD to become a useful tool in treating depression and other diseases containing neural atrophy.

Microdosing

In recent years, the practise of microdosing LSD has become more prevalent in western culture. This treatment consists of regular ingestion of sub-threshold (6-25µg) quantities of LSD 2-3 times a week. During his interview in 1976, Albert Hofman recommended using 25 micrograms of LSD, but never named this amount the way the science world does nowadays. Stanislav Grof, the father of psycholytic psychotherapy who used small doses of LSD to

accelerate the effects of sessions, tended to use 100 micrograms. It can not be precisely called micro dosing, so it has to be noticed that this kind of practice is quite new [35].

Microdosing is not meant to induce perceptual alterations [36]. Instead, the intended purpose is to increase creativity and energy levels, and improve mood, focus and creativity. It can also give a relief of pain, anxiety, and depression.

Unfortunately, it has not been scientifically tested whether microdosing can be effectively used as a treatment of psychiatric disorders. Furthermore, there are reported negative outcomes of this kind of treatment- such as migraines or fear. Serotonergic drugs, after 6 weeks of taking, can also cause frustration. Furthermore it has to be noticed that overdosing the daily amount of LSD can lead to unintended "trips" [36].

LSD for treatment of alcoholism, terminal illness-associated anxiety, opioid use, depression and cluster headaches

LSD and LSD-associated psychotherapy were seriously investigated in the 1950-the 1960s to treat anxiety associated with terminal cancer, alcoholism, opioid use disorder, and depression. The results of these first studies were very promising: In short, anxiety was reduced for two months after two doses of LSD in patients with anxiety associated with a life-threatening disease, and moreover, no side effects were noticed in medical settings. This data led to further investigations of the therapeutic potential of LSD in psychiatry. Nowadays, LSD is a well-studied pharmacological substance, with more than 1000 published reports. According to one of them 'It increases ratings on all dimensions and subscales of the 5-dimension altered states of consciousness (5D-ASC) scale that has been used in all modern studies. Furthermore, evaluations of subjective experiences suggest facilitated access to emotions, confrontation of previously unknown anxieties, worries, resources & intense emotional peak experiences as major psychological working mechanisms.' These experiences could change the world view, thereby habits, lead to situational understanding, and overhaul one's emotional trust [37].

Lately, LSD has been taken under investigation again to assist psychotherapy on anxiety in 11 participants with life-threatening diseases (eight of them with cancer). [The trial assessed the effects] Eleven of 12 patients, who were administered the experimental drug (treated) were LSD-naive. 'Eight patients received 200 µg (this amount provide an experience that is well psychologically manageable for the first contact with this substance) LSD twice, and three patients received active placebo (a low dose of 20 µg LSD) twice in two sessions 2–3 weeks

apart, with an open-label crossover to 200 µg LSD after the first randomized, double-blind treatment phase.' At the beginning of the study, all of the participants presented higher ratings of anxiety on the state-trait anxiety inventory (STAI). Six had a diagnosis of generalized anxiety disorder, and seven were diagnosed with major depression. The study revealed (described) a significant decrease in STAI anxiety 2 months after the two LSD sessions compared with baseline anxiety scores. However, most of the attendees expressed a desire for more than two LSD sessions and a longer therapy. This is consistent with the study's final results, indicating that at least two LSD sessions are needed to demonstrate desired effects because decrease in STAI score was more prominent after the second LSD session. The placebo group didn't admit any decrease in STAI scores (but noted that the placebo control group was too small for statistical comparisons with the treatment group - valid control missing). Furthermore, none of the attendees reported lasting adverse reactions. The benefits were sustained over time, a follow-up study at 12 months in nine patients reported decreases in anxiety at the level of 77,8% and an increase in quality of life around 66,7%, regretfully the follow-up lacked a control group, too. More to the point still no drug-related severe complications of the administration (adverse effects) were reported, excluding panic reactions or related to neither general medical conditions nor psychiatric such as flashback phenomena or other prolonged negative effects

For those much more curious and engrossed in this unputdownable topic - a larger trial that uses LSD in patients who suffer from anxiety associated with severe somatic disease and anxiety disorder is conducted in Switzerland (NCT03153579).

In conclusion, even a few single administrations of LSD or related substances in a medically supervised therapeutic setting may be safe and beneficial for patients with anxiety associated with severe disease, depression, or addiction. However, these old–new treatments seem to be potent, especially in the field of psychiatry. Therefore, it's our responsibility as professionals to carefully study these new options and attempt to be up-to-date with these cures as alternative solutions so patients in despair will not reach for under-the-counter treatments from illegal sources. As all above-mentioned indicates, more 'methodologically sound research on the psychological and biological mechanisms and therapeutic potential of LSD in psychiatry is needed' [38,39].

LSD (single use or a few doses) is also reported to lessen cluster headache and induce remission more effectively than the standard treatment. The participants for this finding were recruited from cluster headache websites and headache clinics. The conclusive analysis included responses from 496 sufferers. The lysergic acid diethylamide, lysergic acid amide and

other psychedelic experimental drugs were comparable to or more efficacious than most traditional medications. These agents were also perceived more effective in shortening or aborting a cluster period and bringing chronic cluster headaches into remission than conventional medications. Furthermore, infrequent and non-hallucinogenic doses were reported to be efficacious. Findings provide additional evidence [40].

Summary

LSD, a drug with big stigmatization, may be surprisingly helpful in the treatment of psychiatric diseases. It is worth remembering that it does not activate the dopaminergic reward system, so it can not be addictive. Considering the benefits of using this substance, such as spiritual enlargement, stress reduction, or mood improvement, it seems like a cure worth trying. The toughest and the most important way to make it officially registered is the destigmatisation of psychedelics. Fortunately, more countries appreciate the low medical doses as a treatment. Perhaps soon, the world's mindset would change, and this kind of treatment might be conducted.

References

1. Nichols D.E.: Psychedelics. Pharmacological Reviews April 1, 2016, 68 (2) 264-355.
2. Baumeister D., Barnes G., Giaroli G., Tracy D.: Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. Therapeutic advances in psychopharmacology, 2014, 4(4), 156–169.
3. Berger M., Gray J. A., Roth B. L.: The expanded biology of serotonin. Annual review of medicine, 2009, 60, 355–366.
4. Carhart-Harris R.L, Nutt D.J.: Serotonin and brain function: a tale of two receptors. Journal of Psychopharmacology., 2017, 31(9), 1091-1120.
5. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England), 2018, 392(10159), 1789–1858.
6. Ferguson J.M.: SSRI Antidepressant Medications: Adverse Effects and Tolerability. Primary care companion to the Journal of Clinical Psychiatry, 2001, 3(1), 22–27.

7. Cowen P.J., Browning M.: What has serotonin to do with depression? World psychiatry: official journal of the World Psychiatric Association (WPA), 2015, 14(2), 158–160.
8. Inserra A., De Gregorio D., Gobbi G.: Psychedelics in Psychiatry: Therapeutic Mechanisms. Pharmacological Reviews, 2021, 73(1), 202-277.
9. Greiner T., Burch, N.R., Edelberg R.: Psychopathology and psychophysiology of minimal LSD-25 dosage; a preliminary dosage-response spectrum. AMA Archives of Neurology and Psychiatry, 1958, 79(2), 208–210.
10. Martin R., Schürenkamp J., Gasse A., Pfeiffer H., Köhler H.: Determination of psilocin, bufotenine, LSD and its metabolites in serum, plasma and urine by SPE-LC-MS/MS. International Journal of Legal Medicine, 2013, 127(3), 593–601.
11. Britannica Encyclopedia. LSD. https://www.britannica.com/science/LSD (cited 05.04.2021).
12. Jonas S., Downer J. de C.: Gross behavioural changes in monkeys following administration of LSD-25, and development of tolerance to LSD-25. Psychopharmacologia, 1964, 6(4), 303–306.
13. Lüscher C., Ungless M.A.: The mechanistic classification of addictive drugs. PLoS Medicine, 2006, 3(11), 437.
14. Nichols D.E.: Hallucinogens. Pharmacology & therapeutics, 2004, 101(2), 131-181.
15. Dolder P. C., Schmid Y., Haschke, M., Rentsch K.M., Liechti M.E.: Pharmacokinetics and concentration-effect relationship of oral LSD in humans. The International Journal of Neuropsychopharmacology, 2015, 19(1), 72.
16. Halpern J.H., & Pope H.G., Jr.: Hallucinogen persisting perception disorder: what do we know after 50 years? Drug and Alcohol Dependence, 2003, 69(2), 109–119.
17. Majić T., Schmidt T.T., Gallinat J.: Peak experiences and the afterglow phenomenon: when and how do therapeutic effects of hallucinogens depend on psychedelic experiences? Journal of Psychopharmacology, 2015, 29(3), 241–253.
18. Hofmann A.: LSD - My Problem Child. 1. How LSD Originated http://www.psychedelic-library.org/child1.htm (cited 12.05.2021)
19. Brecher, E. M. The consumers union report on licit and illicit drugs, 1972. https://www.druglibrary.org/schaffer/Library/studies/cu/CU50.html (cited 14.06.2021).
20. Lee M.A., Shlain B.: In the beginning there was madness… [in:] Acid dreams: The complete social history of LSD: The CIA, the sixties, and beyond. Lee, M. A., & Shlain, \

B. Grove Press, New York, 1992, 3-26.

21. Terry Gross: The CIA's Secret Quest For Mind Control: Torture, LSD And A 'Poisoner In Chief'.https://www.npr.org/2019/09/09/758989641/the-cias-secret-quest-for-mind-control -torture-lsd-and-a-poisoner-in-chief (cited 15.06.2021)
22. Dyck E.: Flashback: psychiatric experimentation with LSD in historical perspective. The Canadian Journal of Psychiatry, 2005, 50(7), 381-388.
23. Buckman J.: LSD— Psychiatric Therapy And Research. [in:] Psychedelic Reflections. Lester Grinspoon, MD and James B. Bakalar, JD: Human Sciences Press, New York, 1983, 153-163.
24. Ustawa z dnia 31 stycznia 1985 r. o zapobieganiu narkomanii. http://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU19850040015 (cited 24.07.2021).
25. Obwieszczenie Marszałka Sejmu Rzeczypospolitej Polskiej z dnia 27 października 2020 r. w sprawie ogłoszenia jednolitego tekstu ustawy o przeciwdziałaniu narkomanii. http://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20200002050 (cited 24.07. 2021).
26. Rozdział 7 - Przepisy karne - Przeciwdziałanie narkomanii. - Dz.U.2020.2050 t.j.. https://sip.lex.pl/akty-prawne/dzu-dziennik-ustaw/przeciwdzialanie-narkomanii-172194 65/roz-7 (cited 24.07.2021).
27. Cornwell B. i Linders A.: The Myth of «Moral Panic»: An Alternative Account of LSD Prohibition, Deviant Behavior - DEVIANT BEHAV 23. https://doi.org/10.1080/01639620290086404 (cited: 24.07.2021).
28. Convention on Psychotropic Substances, 1971. https://web.archive.org/web/20120415011336/http:/www.unodc.org/pdf/convention_1971_en.pdf (data pobrania 24.07. 2021).
29. Česká psychedelická společnost. https://czeps.org/en/research/current-research-in-nimh-czech-republic/ cited 24.07.2021).
30. Polskie Towarzystwo Psychodeliczne. http://psychodeliki.org (cited 24.07.2021).
31. Česká psychedelická společnost. https://czeps.org/en/research/current-research-in-nimh-czech-republic/ (cited 24.07.2021).
32. Calvin Ly: Psychedelics Promote Structural and Functional Neural Plasticity. citedhttps://www.cell.com/cell-reports/fulltext/S2211-1247(18)30755-1?fbclid= IwAR 0i m M sKZ1m46o1IF3bHtKyuqwmGPZ5lJ0Cg0-zM25vOBD79uY6iS6_f-k (cited 07.04.2021

33. Nadia R. P. Hutten: Low Doses of LSD Acutely Increase BDNF Blood Plasma Levels in Healthy Volunteers. https://pubs.acs.org/doi/10.1021/ acsptsci.0c00099? fbclid= IwAR2L-0c6VaVZ0Rb3y9MqSkEqLfjrtfYH7Lc5kbWeuJYa9xYgGXg041OOTwI& (cited 04.07. 2021).
34. Siresha Bathina: Brain-derived neurotrophic factor and its clinical implications. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697050/ (cited 26.07.2021).
35. Polito V., Stevenson R.J.: A systematic study of microdosing psychedelics. PLoS One, 2019, 14(2), e0211023.
36. Hutten NRPW, Mason N.L., Dolder P.C., Kuypers K.P.C.: Motives and Side-Effects of Microdosing With Psychedelics Among Users. International Journal of Neuropsychopharmacology, 2019, 22(7), 426–434.
37. Liechti M.E.: Modern clinical research on LSD. Neuropsychopharmacology, 2017, 42(11), 2114-2127.
38. Gasser P., Kirchner K., Passie,T.: LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. Journal of Psychopharmacology, 2015, 29(1), 57-68.
39. Gasser P., Holstein D., Michel Y., Doblin R., Yazar-Klosinski B., Passie T., & Brenneisen R.: Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. The Journal of nervous and mental disease, 2014, 202(7), 513.
40. Schindler E.A., Gottschalk C.H., Weil M.J., Shapiro R.E., Wright D.A., & Sewell R.A.: Indoleamine hallucinogens in cluster headache: results of the Clusterbusters medication use survey. Journal of Psychoactive Drugs, 2015, 47(5), 372-381.

Past drug addiction and the daily life and health of addicts and their families

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Introduction

A man from the beginning of history tried to flee from the sad, terrible reality of the world around him. However, unfortunately, his efforts to change his mind eventually led to finding and using narcotic substances. The history of these substances dates back to the times of Sumerian civilization. Seven hundred years before the birth of Christ, descriptions of the cultivation and preparation of opium were made. At first, the intoxicating properties of various products of plant origin were used in the religious rites of the first civilizations: Sumerian, Egyptian, Indian and Chinese. Then, with the widespread use of psychoactive substances, the first mentions of the medics of the late effects of their chronic and excessive use began to appear.

Marek Aurelius was probably the first person to be described as an addict to opium. Literature has shown considerable evidence of the widespread use of drugs. Homer cited a description of a poppy drink that causes oblivion. Marco Polo's diary mentions the cannabis extract used by Persian during the religious fights [1].

Another aspect of psychoactive effects was their analgesic properties. Three thousand years ago, in Thebes, opium was a painkiller. In the 16th century, Paracelsus introduced a widely used opium tincture in healing. By the end of the 19th century, the addictive properties of laudanum were not known. Only at the end of that century was it replaced with morphine, which also had addictive properties. The next drug used in treating the drug addiction of opium and morphine was heroin used as an antitussive recommended mainly in infants. In 1913 appeared the first reports about the addictive properties of heroin. In the twenties, its market

access was limited. In 1927 amphetamine was introduced into the treatment under benzedrine, which was used as a remedy for asthma. In 1936, an amphetamine addiction syndrome was described. In 1941 it was placed on the list of drugs (Germany), and after 1945 found to treat depression, obesity, Parkinson's disease, and others [2].

Stanisław Górski writes in one of the books that the wave of drug addiction began with the publication of A. Huxley's book Doors of Perception and two publications by the then-current professor of psychology at Harvard University T. Leary'ego. Both of them were translated into Polish. The drug addicts were reading the text in which the advertising of drugs was hidden [3].

Drug addiction spread on all continents, and rapid economic, social and cultural transformation and the opening of country borders contributed to this phenomenon's accelerated development. Drug addiction is a severe social and economic problem. The consumption of narcotic drugs gives the feeling of independence, illusory freedom, and pleasure. Unfortunately, after a short period, reality returns with everyday problems. A man who cannot, or does not want to do, will again seek the chance to escape into the world of illusion. In this way, it comes to addiction. Over time, the body demands more and more doses of addictive substances, without which it can no longer function properly.

Definition of drug addiction

Drug addiction is a term referring to addiction to chemicals that affect brain activity. It is assumed that a drug is a chemical compound or a mixture thereof that is not used for health purposes, and at the same time, makes a change in the biological and mental functions of a human being [4].

Ruth Maxwell defines addiction as "losing control, crossing the invisible border between desire and need for drugs," pointing out that this boundary can only be crossed once.

Drug addict – a person dependent on any drug [5]. According to the World Health Organization (WHO) addicted has the following features:

- the compulsion to take a measure,
- a constant tendency to increase the dose,
- mental addiction, often physical,
- harmful effects of drug use on individuals and society [6].

Drugs

The WHO divided drugs into the following categories: opioid drugs, psycho-stimulators, cocaine, marijuana and hashish, hallucinogens, inhaled substances, and drugs and barbiturates, nicotine, alcohol, steroids.

The study aimed to assess the impact of drug abuse on the daily lives and health of addicts and their families.

Materials and methods

The study covered 40 people aged 22–36 from the Anonymous Drug Addiction Club and the Good Shepherd Center in Silesia. The criteria for inclusion in the study group were past treatment and at least one year of abstinence. Data was collected using the original questionnaire.

Results

The general characteristics of the examined group are shown in Table I.

Table I. General characteristics of the examined group

Study group n = 40 (100%)			
Variable	**n**	**%**	
Sex	25	62,5	Men
	15	37,5	Women
Age	33	82,5	22-30 years
	7	17,5	31-36 years
Place of residence	40	100	Town
	0	0	Village
Education	9	22,5	Basic education
	25	62,5	Secondary education
	6	15	Higher education
Marital status	7	17,5	Bachelorette
	14	35	Bachelor
	10	25	Married man
	5	12,5	Married woman
	3	7,5	Divorcee

The study group of addicts included a total of 40 people (100%). Among them were 37.5% women and 62.5% men. The majority of the group were people aged 22–30 (82.5%). All the residents were city dwellers. The highest percentage of addicts were people with secondary education (62.5%). However, only 15% of respondents declared higher education. In the study group, 52.5% were single. Among respondents, 37.5% were married, and 7.5% of them were divorced.

During treatment, 27.5% of addicts decided to change their current place of residence in order to break up with the current environment.

The characteristics of the examined group taking into account the course of addiction are presented in Figure 1.

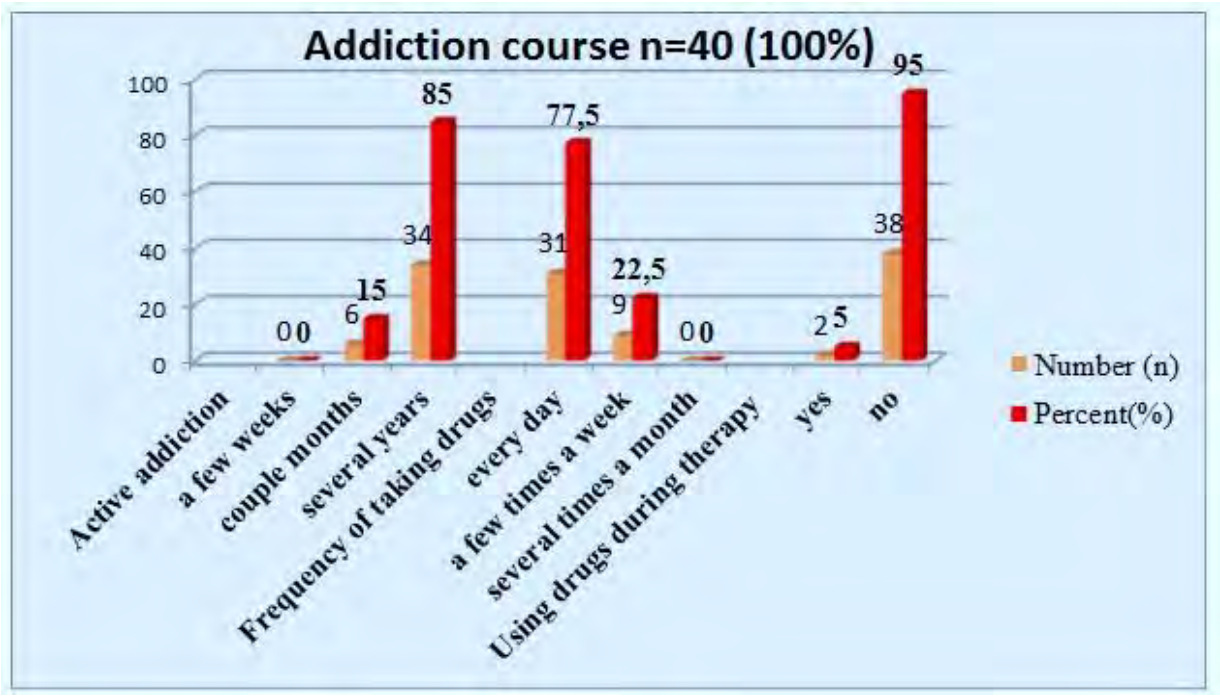


Figure 1. Characteristics of the examined group taking into account the course of addiction

In the study group, 85% were people who had been addicted for several years. As many as 15% of the interviewees have declared few months of addiction. Moreover, 77.5% of respondents admitted to daily use of narcotic drugs, while the remaining 22.5% of respondents confirmed drug use several times a week. Only 5% of the respondents used drugs during therapy.

Characteristics of the test group, taking into account the knowledge about the effects of drug use, is shown in Figure 2.

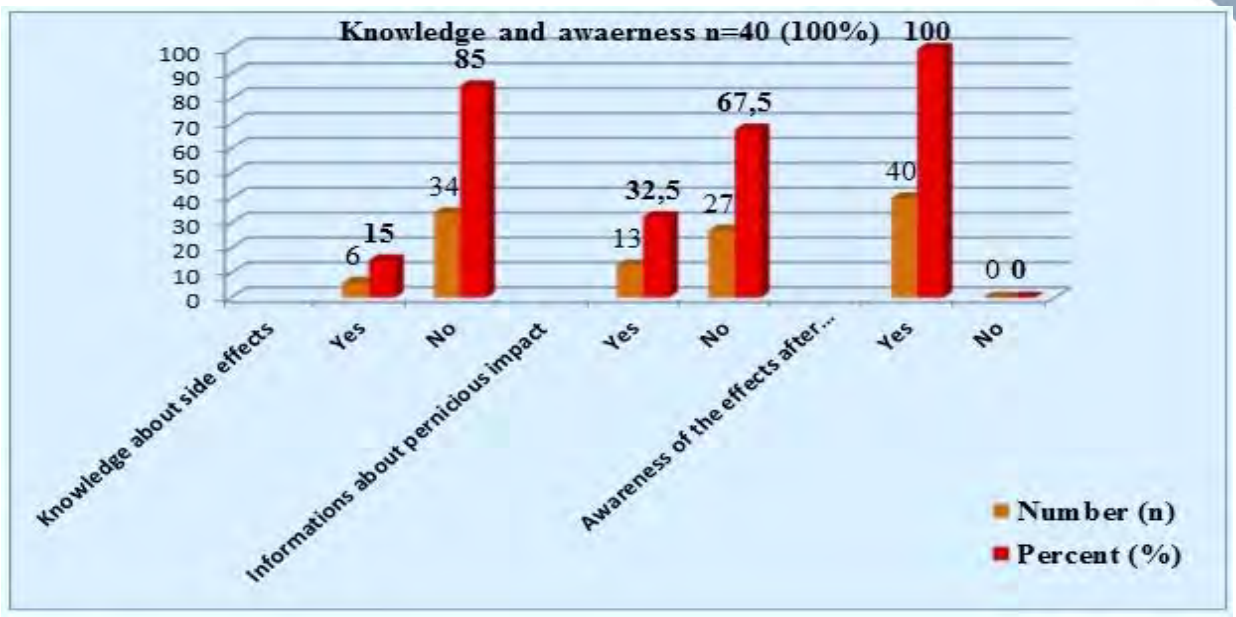


Figure 2. Characteristics of the test group, taking into account the knowledge about the effects of drug use

Among the respondents, the largest group was those who started using psychoactive substances without knowing their side effects. They represented 85% of all respondents. Almost 1/3 admitted that they had contact with information about the harmful effects of drugs. However, after therapy, all respondents declared knowledge of the harmful effects of drugs on the organism.

Characteristics of the study group, taking into account the way drug supply is shown in Figure 3.

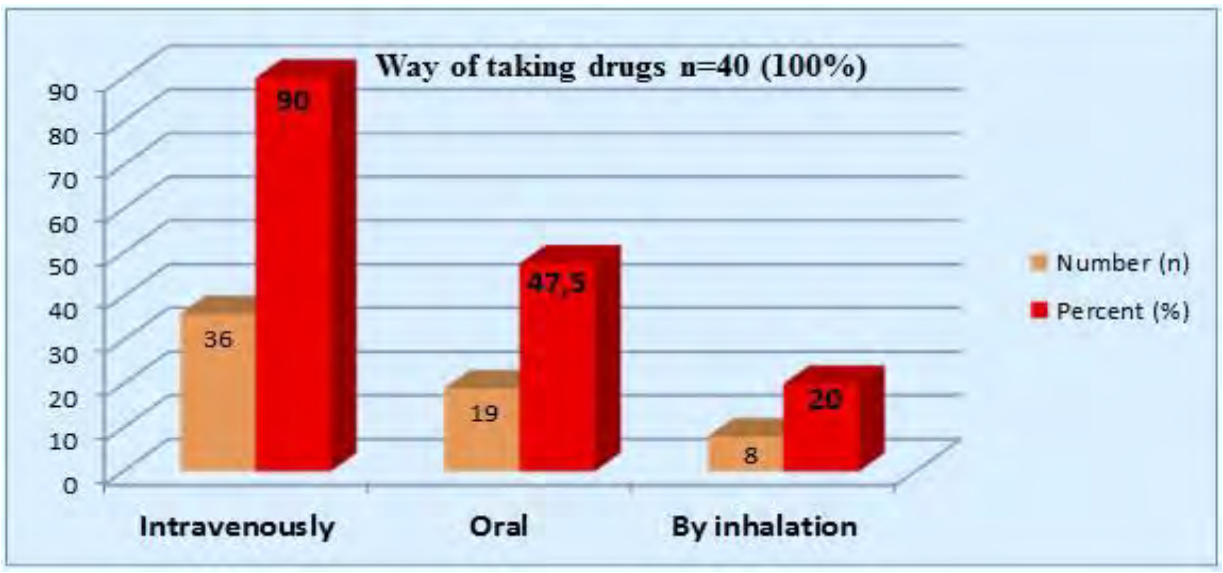


Figure 3. Characteristics of the study group, taking into account the way drug supply

Addicts were taking drugs in different ways. The highest number, as many as 90%,

admitted that addictive substances were taken intravenously, and 47.5% also used oral addictive forms (including alcohol). Conversely, the lowest number of addicts were taking psychoactive substances by inhalation – 20% of all respondents.

The characteristics of the examined group taking into account the types of addictive substances, are presented in Figure 4.

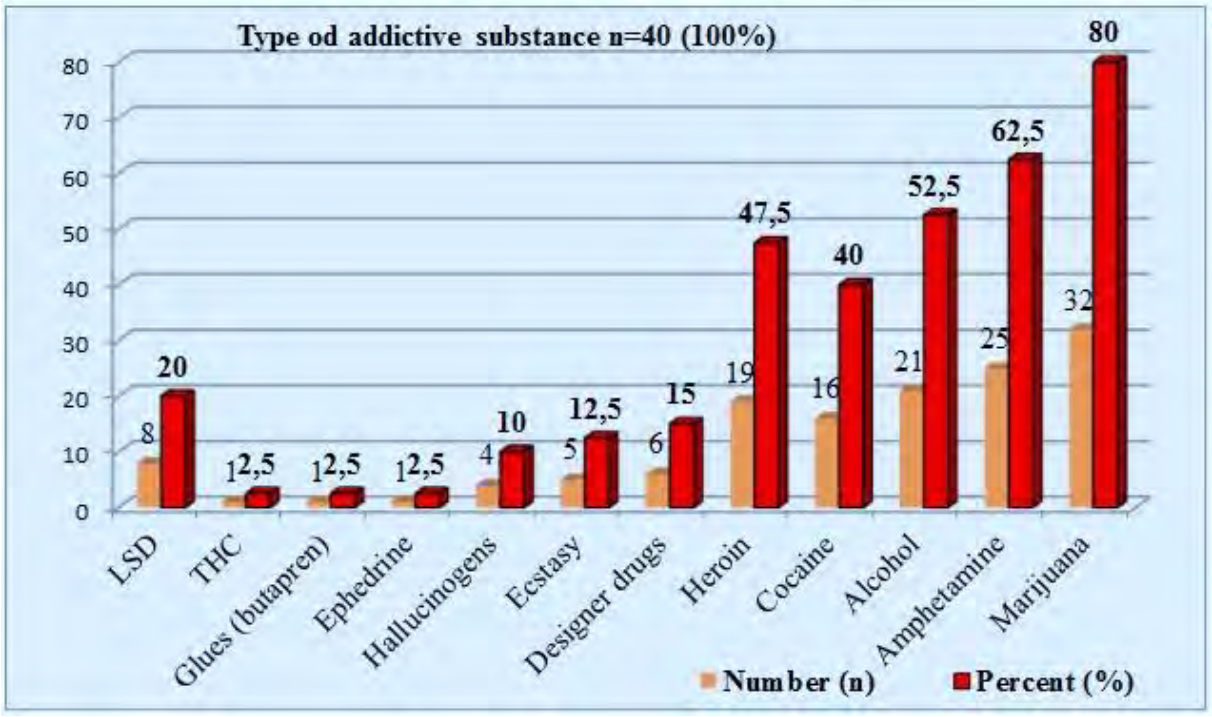


Figure 4. Characteristics of the examined group taking into account the types of addictive substances

According to the data obtained, the most commonly used drugs were (in descending order): marijuana 80%, amphetamines 62%, alcohol 52%, heroin 47.5%, 40% cocaine, and 20% LSD.

The characteristics of the study group, including the duration of treatment, the time since its completion, and its possible continuation, are presented in Figure 5.

Participants in the study reported in 55% of cases that the treatment process was prolonged, and it even ran for several years. In 15% of them, the therapeutic process has not yet been completed. In 20% of the interviewees have passed a few years after the end of therapy, and 5% indicated that they had completed the treatment just two weeks earlier.

Characteristics of the study group taking into account the source of the support received and interpersonal contacts are shown in Figure 6.

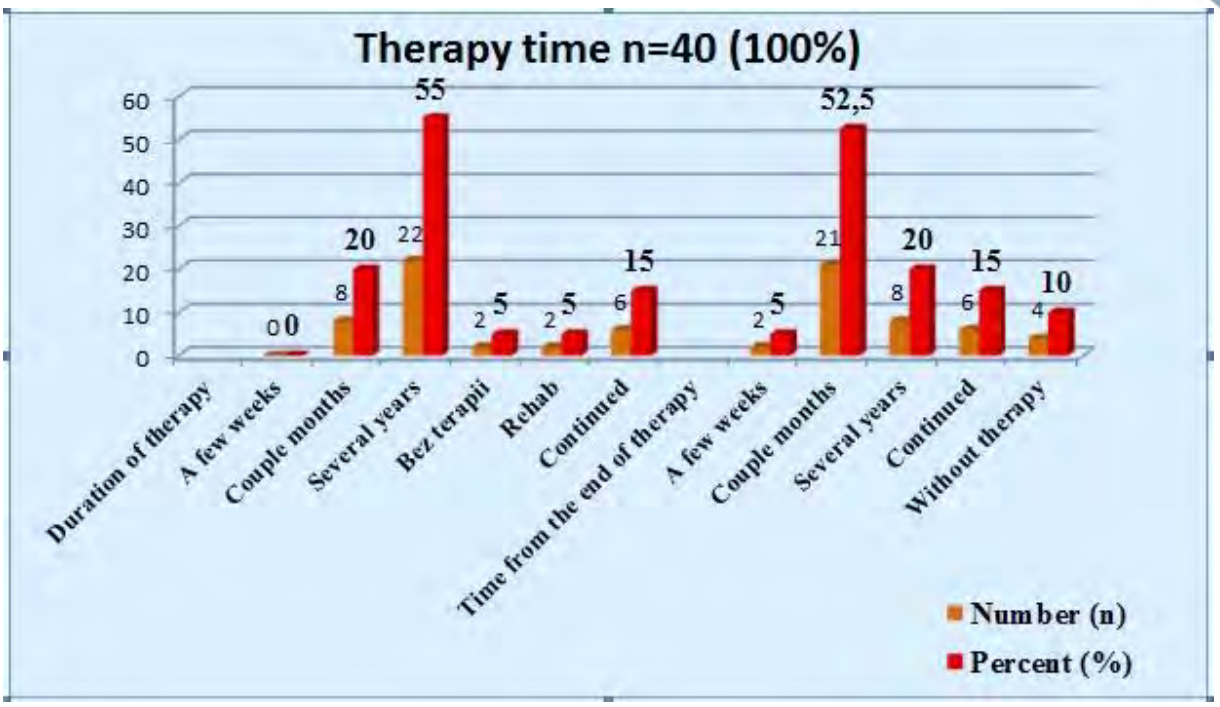


Figure 5. Characteristics of the study group, including the duration of treatment, the time since its completion, and its possible continuation

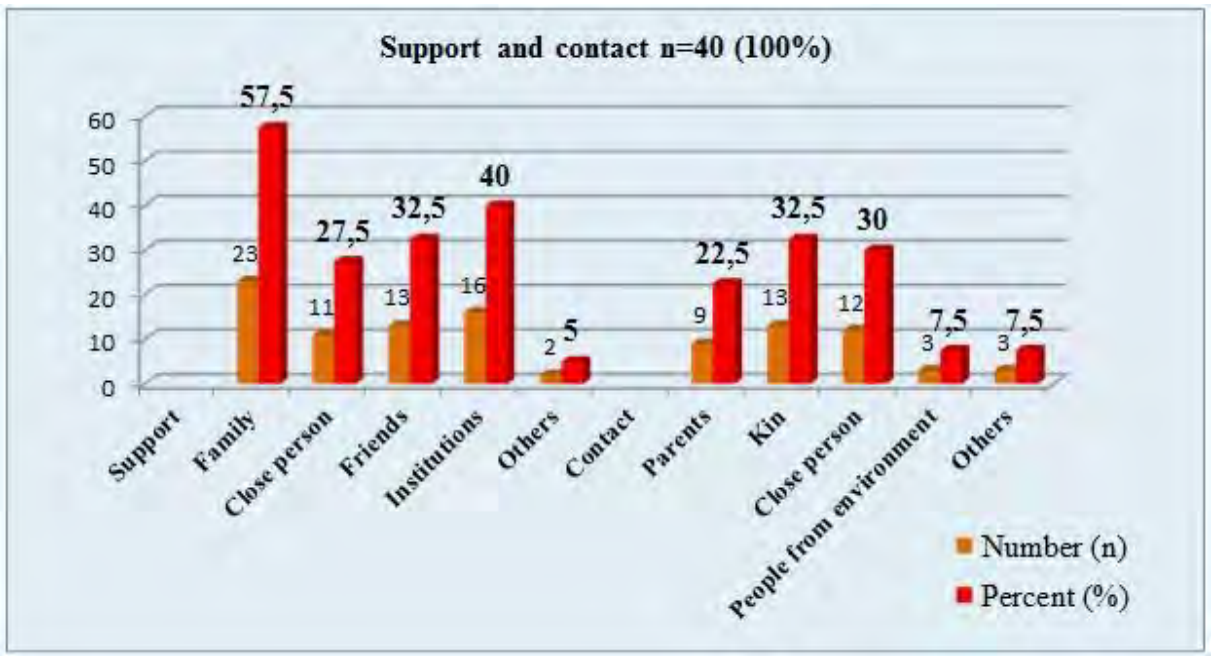


Figure 6. Characteristics of the study group taking into account the source of the support received and interpersonal contacts

During therapy, 57.5% of the respondents received family support. It is worth noting that stressed that 40% of the respondents indicated help from various institutions. Friends

supported 32.5% and close relatives – 27.5% of respondents. Addicts kept in contact with kins, relatives, and parents respectively in 32.5%, 30%, and 22.5% of the cases. A small proportion (7.5%) of the respondents maintained contact with people who were drug addicts.

Characteristics of the study group taking into account the factors influencing the therapy are shown in Figure 7.

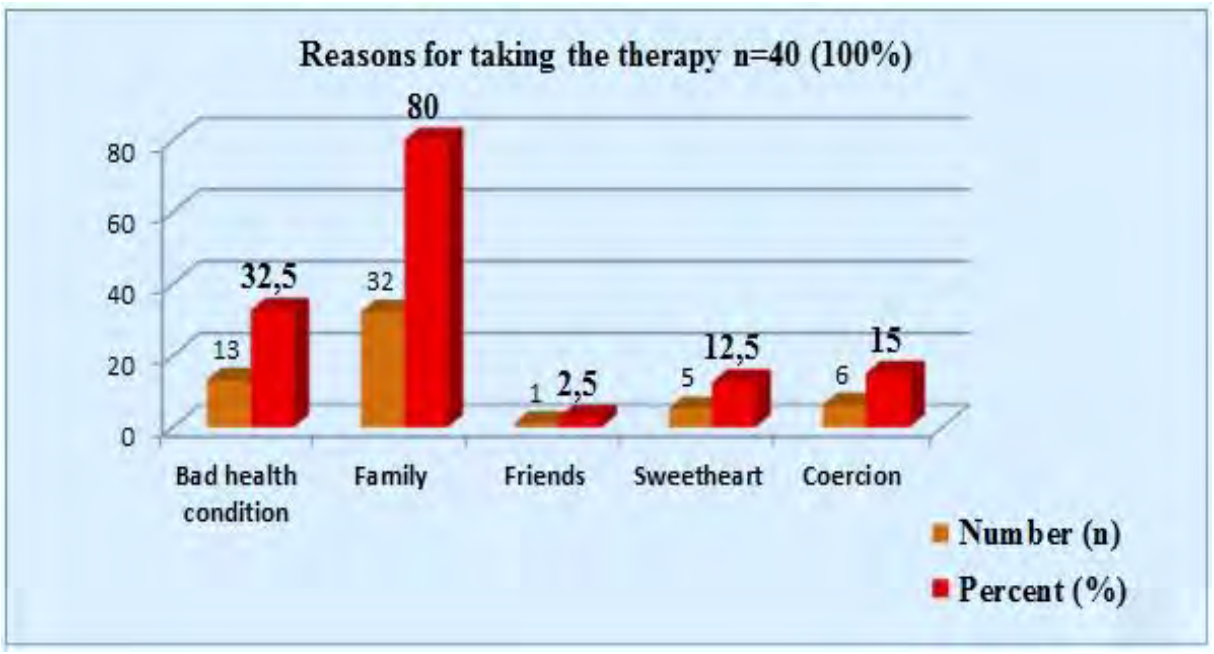


Figure 7. Characteristics of the study group taking into account the factors influencing the therapy

One of the most important factors affecting addicts to take therapy was a bad state of health (32.5% of respondents). Up to 80% felt that the family had had the greatest impact on decisions about their treatment. In 15% of cases, the trigger factor was a compulsion, in 12.5% of girlfriends and 2.5% of the friends.

After completing therapy, 67.5% of respondents took up the job, and 42.5% took up the study. Respondents asked about earlier school problems in 67.5% of cases gave a negative response. Unidentified problems in the school were reported by 17.5%, and 15% of the respondents indicated only some school subjects. With therapy, 90% of respondents considered themselves cured, 25% changed their lifestyle, and 15% changed their environment.

Characteristics of the study group about lifestyle after therapy are presented in Table II.

After treatment for drug addiction, the study group indicated in 90% of all respondents that the therapy was sufficient. Self-esteem recovered 95% of respondents. In the study group,

most people under the influence of narcotics had mental and nervous disorders (77.5%). Penalties accounted for 42.5% of the study participants. For treatment at the Psychiatric Ward, 27.5% of the respondents were admitted in the survey.

Characteristics of the examined group of addicts after treatment, including the desire to have family and offspring is presented in Table III.

Table II. Characteristics of the study group with regard to lifestyle after therapy

Lifestyle after therapy Number of the study group n-40 (100%)		
Variable	**n**	**%**
Undertaking study	17	42,5
Taking a job	27	67,5
Change of environment	6	15
Change of lifestyle	10	25
Sense of recovery	36	90
Regaining self-esteem	38	95

Table III. Characteristics of the examined group of addicts after treatment, including the desire to have family and offspring

Study group n=40 (100%)			
Variable	n	%	
Planning to starting a family	24	60	YES
	4	10	NO
Having a family	12	30	YES
	28	70	NO
Having children	16	40	YES
	24	60	NO
Planning offspring	19	47,5	YES
	5	12,5	NO

60% of all respondents reported plans for starting a family, and 30% of them already had their own family. Of all the respondents, 47.5% planned to have children, and 40% already had children. Respondents were asked whether they were related to drug addicts. In 70% of the cases a negative response was received and 10% of the respondents admitted that the partner

was addicted to drugs. The study revealed that more than half of the respondents had siblings (57.5%). None of the respondents came from a large family.

In many families, there were different addicts. Nicotine was first (32.5%) and second alcoholism (17.5%). Drugs as an addiction occurred in 2.5% of cases. Unemployment concerns 30% of the families of the study group. In 42.5% of families, both parents worked. Only the mother (17.5%) or only the father (10%) worked in other families.

Characteristics of the examined group taking into account the cause of addiction is presented in Figure 8.

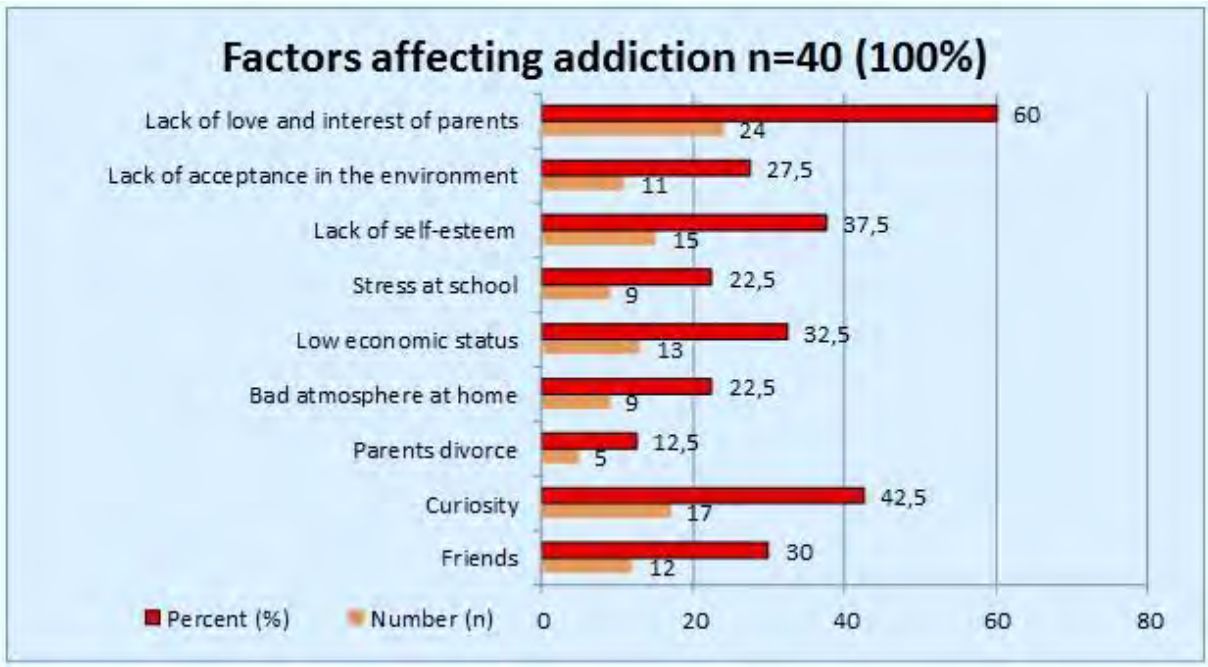


Figure 8. Characteristics of the examined group taking into account the cause of addiction

The questionnaire indicated that there was a significant influence on addiction: lack of parental love and interest (60%), curiosity (42.5%), and self-deprecation (37.5%). Almost 1/3 (32.5%) of the respondents emphasized their low economic status, while 22.5% complained about the bad atmosphere at home. In 92.5% of respondents, there was an interest in addiction in schools.

The possibility of protection against drug addiction by a valid form of communication indicated 77.5% of respondents. As much as 67,5% of participants pointed out brochures as the best and most effective form of communication.

The characteristics of the study group, taking into account the effectiveness of conducting drug education in school education, are presented in Figure 9.

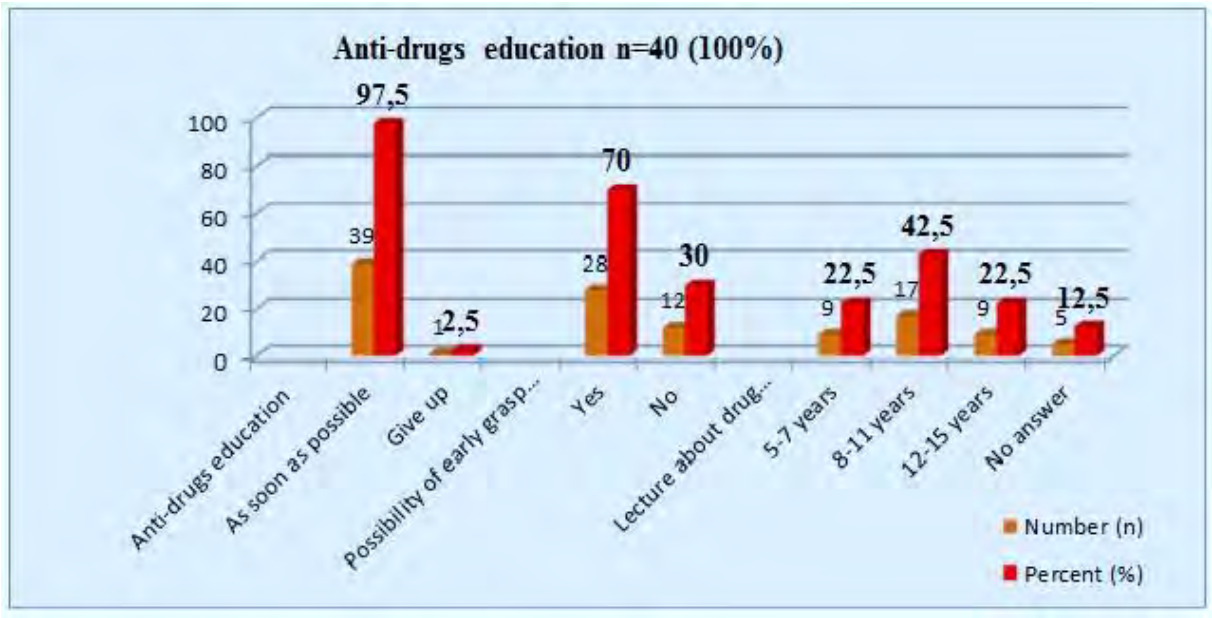


Figure 9. Characteristics of the study group, taking into account the effectiveness of conducting drug education in the course of school education

Respondents in 97.5% believed that education to warn against drug use should be carried out, starting at the earliest. In addition, 70% of respondents believed that it was possible to capture the problem of complete addiction. A good age to start conversations, education of children according to 42.5% of respondents is the age range is between 8–11 years, while 22.5% indicated age 5–7 years and the same percentage for age 12–15 years. 12.5% of respondents had no opinion.

Discussion

Based on a study carried out in a 40-person group that was a year or more after the treatment of narcotic addiction, efforts to answer questions about their future lives were made. Note on attempts to modify life, learn, fill the gaps in education, or work to keep up with own money was on.

The study results showed that most respondents received help from relatives, families, institutions and that they could count on the help of the public. Despite the current knowledge about drug addiction, it is still not possible to master the wave of this phenomenon. Addicts who undertake the therapy must have support from the family or institution and society as a whole. Drug users are often adolescents seeking adventures. The study found that most of the examined group of addicts were male (62.5%), which may indicate their greater susceptibility

to external factors. All the respondents came from the city and fit into in the age range of 22–36 years. They most often were from families with one or two children (57.5%). 12.5% of the respondents admitted that they had a drug problem in their families and most often referred to siblings. There were also addictions from other substances: tobacco (32.5%), alcohol (17.5%), and narcotics (2.5%). In most families of addicts, there was not the economic aspect of the problem. These data may indicate another source causes of addiction. Young people used to take addiction for the first time without realizing the side effects of their long-term use. The lack of awareness in this area can be attributed to the fact that 85% of the respondents did not know the side effects of drug use before, and only 32.5% of respondents were aware of the harmful effects of drugs on the body. Despite this, they began to reach for such substances. We say about active addiction when the body can no longer function without supplying the drug to the body over an extended period. Most addicts have to take drugs every day and at all costs. Such a condition can last up to several years. A quick break with addiction and specialized treatment makes it easier to fight it. Drugs abuse results in the progression of many diseases, including mental disorders, often affecting conflicts with the law. Of the examined group, 77.5% of all respondents reported psychiatric disorders, of which 27.5% were treated in psychiatric wards. Most respondents took addictive drugs for several months. Very often, a couple of psychoactive drugs were drunk with alcohol. This situation is called the incident "of a substance to pave the way," as Kandel writes and confirms in his observations [7]. According to his observation, there is a repeated scheme of taking three different substances in juveniles, falling on the path to addiction [8]. This phenomenon is quite common. This phenomenon in Poland confirms the studies of Hanusek 1976; Cekiera 1985 and Barańska 1988 [4]. The most commonly used drugs by the study group were: marijuana (80%), amphetamine (62%), alcohol (52.5%), heroin (47.5%), and cocaine (40%). Numerous studies of the authors mentioned above provide similar results. Various available ways to take drugs. The intravenous way (90%) was most preferred. Each of the ways poses a potential danger to the health. The way of intravenous injection carried a particular risk in the context of transmission of the human immunodeficiency virus (HIV), the hepatitis B virus (HBV), and the hepatitis C virus (HCV). Heroin was one of the most problematic drugs, because it brings the first of all rapid and strong addiction. In addition, very bad physical effects and lowering of libido were observed. Kostowski in his observations, confirmed that heroin is highly addictive. The following are listed: alcohol, cocaine, amphetamine, and caffeine. Psychoactive substances are readily available on the market, as evidenced by people from younger and younger generations'

reaching for it. The phenomenon of narcotic addiction can be traced to specific situations of life and the environment. Thus, at least three factors are involved in addiction: "environment – man – drug" [4]. The devastation that drug addiction causes is enormous. This may be evidenced by several thousand people die each year in the European Union due to narcotic substances. According to Kostowski, the majority of them are men aged 20–30. Among the factors predisposing to drug use were: lack of love and interest (60%), the curiosity of new experiences (42.5%), self-deprecation (37.5%) and lack of acceptance in the environment and problems with which the respondents could not cope in everyday life (27.5%). Cekiera has a similar position based on his research considering that "unmet needs, strong conflicts in the family and school environment lead to reaching for a drug" [4]. However, Kandel [7] considers that the family does not contribute directly to the child's drug abuse. The actual role of the family is very complex. Addiction may primarily affect people who effectively avoid taking responsibility for their lives and provoke other family members to take over. It is important to emphasize that the role of a particular person in a family system depends not only on the functioning of the family but also on the individual's personality structure. Addiction is a difficult experience for the whole family and most often completely changes the relationship between its members.

The use of psychoactive substances often led to a slowdown in mental processes, resulting in a low level of education. However, the study results revealed that many people after completion of therapy have taken to supplement their education (42.5%), allowing a total of 62.5% of the study group to attain secondary education. The level of education depends on the level of control of the person and the correct attitude to the world and reality [9].

Problems in dealing with parents and other carers can weaken support and proper adult supervision, thereby increasing the person's vulnerability to the environment and related factors. These two mechanisms: support and control of adults, are critical protective factors during adolescence [10]. An essential element in the fight against drug addiction was therapy. The treatment of young addicts took a very long time, even several years, which was conditioned by many factors. This was related to the type of intake, dosage, exposure route, duration of use, and whether or not there were episodes of recurrence.

Difficulty with drug addiction resulted in re-access to the drug during treatment by 5% of patients, which significantly prolonged the treatment process. However, 90% of the respondents considered that the therapy was sufficient for them and helped them regain their self-esteem (95%). In a study group, both addiction and therapy lasted for several years. It is important that addicts often find support from the family as well and the nearest surroundings,

which allows them to return to reality. In 80% of cases, the family has impacted the treatment and coercion only to a small extent. However, during the same therapy, support from the family has received more than half of the respondents (57.5%). Cekiera, based on her own observations, pointed out that parents are very seldom consistent with their own child during therapy. Only a small group is involved in the process of treatment and psychotherapy [4]. Therapy has positive effects for the participants themselves and society as a whole. Through therapy, the process of positive attainment is strengthened, as during the process of psychotherapy and social reintegration, adolescents adapts to the environment in which they will live and work. It is not just about removing and treating the symptoms that accompany addiction but about the deep transformations of personality. As the results of the study show, more than half of the surveyed plan to start a family and have children, and 30% of respondents have already established a family, and almost half of them had offspring. Similar results of comparative research on the desire to start a family after therapy have not been found in the literature. Most participants in the study group taking the drug for the first time completely did not realize the side effects of psychoactive substances, as indicated by the study results. With the lack of or insufficient information on drugs and conversations in families, the school is bad for juveniles.

However, it appears that over 90% of surveyed respondents indicated that in the schools, there was interest from teachers and educators about addiction. In comparison, 67.5% said that the best sources of such information are brochures. Furthermore, almost 80% of respondents believed that drug addiction could be prevented through appropriate education, begun early enough, at 8–11 years old. So let us work with addicted people to function adequately in society, opening a new chapter in their lives.

Conclusions

1. The lack of family warmth, interest from parents and lack of acceptance in the environment, and the curiosity of new sensations were the main factors that favour the development of addiction from taking narcotics.
2. Effective therapy has allowed individuals to regain self-esteem, continue learning and take a job that allows easier implementation in everyday life.
3. The family, which is the support of addicts, is an important part of both in the process of addiction and its therapy. Starting one's family is an important life goal to help return to normal life and the environment.

4. There is a need for large-scale pro-health activities promoting drug knowledge, which is already in the early years of school.

References

1. Markiewicz A.: Narkotykowe dylematy. Wyd. BOG&ART., Kielce, 1999, 8-11.
2. Woronowicz B.: Uzależnienia. Geneza, terapia, powrót do zdrowia. Wyd. Edukacja Parpamedia, Poznań, 2009,410-5.
3. Górski S.: Uwaga rodzice – narkomania. Instytut Wyd. Związków Zawodowych, Warszawa,1985, 21.
4. Cekiera Cz.: Psychoprofilaktyka uzależnień oraz terapia i resocjalizacja osób uzależnionych. Wyd. Towarzystwo Naukowe KUL, Lublin, 1988, 23.
5. Dodziuk A, Kamecki W.: Trudna nadzieja. Wyd. Państwowa Agencja Rozwiązywania Problemów Alkoholowych, Warszawa, 1996, 17.
6. Radochoński M.: Podstawy psychopatologii dla pedagogów. Wyd. Uniwersytetu Rzeszowskiego, Rzeszów, 2001, 85-121.
7. Kandel D., Yamagucki K., Chen K.: Stages of progresion in drug involvement from adolescence tu adulthood: further ewidencefor the Gateway Theory. Journal of Studies on Alcohol., 1992, 53(5), 447-457.
8. Serwis uzależnień. www.meet.free.ngo.pl (cited: 15.05.2011).
9. Stankowski A., Stankowska N.: Wybrane problemy patologii społecznej i resocjalizacji. Wyd. Uniwersytetu Śląskiego w Katowicach, Katowice, 2006, 15-26.
10. Uziałło J.: Biologiczne podstawy uzależnień. Biuletyn Serwis, 2009, 46(2), 20-25.

Neuroimmunology and transmission disorders in the pathogenesis of schizophrenia in the context of the diathesis-stress model

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Introduction

Schizophrenia is a debilitating psychiatric disorder characterized by positive symptoms (delusions, hallucinations, disorganized speech and behaviour), and negative symptoms (apathy, diminished affect, and social isolation). It's nowadays classified as a psychotic disorder independently by both DSM and ICD criteria; nonetheless, it's highly required to widen its view to applying the proper treatment cause this condition is mainly about cognitive disorders. Though even Kraepelin, in 1893, defined it as 'dementia praecox', and Bleuler also classified delusions and hallucinations as secondary symptoms. The fact essential to mention is that the degree of deterioration of cognitive functions is a prognostic factor during schizophrenia course. The disease heritability is estimated at ~50% based on concordance rates in monozygotic twins. However, risk profile scores constructed from alleles associated with schizophrenia explain only ~7% of the variation in the liability to schizophrenia. This suggests that genetics cannot fully explain its etiology, so other contributing factors, especially the environmental ones, need to be carefully explored.

Moreover, many independent factors are likely to contribute to the development of schizophrenia. However, these results should be interpreted with caution due to the small number of cases. Studies in Helsinki and Denmark have found that people whose mothers were exposed to the 1957 influenza epidemic during the second trimester of fetal development have a significantly increased risk of developing adult schizophrenia. This finding has suggested an intriguing new hypothesis, containing the impact of viruses, in the study of schizophrenia the etiology of schizophrenia. 'It has suggested the possibility that disturbances of brain development during gestation may contribute to the risk of adult schizophrenia.' Moreover,

children exposed in the second trimester had a significantly higher rate of definite influenza infection (86.7%) in that period compared to those who were exposed during the first and third trimesters (20.0%) [1].

Schizophrenia is nowadays classified as a psychotic disorder independently by the Diagnostic Statistic Manual and International Classification of Diseases criteria. Furthermore, it has always been marked as one of the main categories of mental illness in both systems. As new editions are published, the criteria become decreasingly different from each other. A good example is measuring subtypes of schizophrenia in the latest versions of ICD and DSM and eliminating Schneider's first rank symptoms from both systems [2]. According to the latest installment of the ICD, schizophrenia might be classified using positive symptoms (psychotic and disorganization), negative symptoms (such as flat affect, anhedonia, alogia etc), cognitive symptoms, symptoms of mania or depression, and psychomotor disturbances. Based on those six criteria, the diagnosis may be made, thereby treatment and prognosis can be laid down [2]. Nevertheless, neither ICD nor DSM present the etiology of schizophrenia and focus on its neurobiological disturbances.

To date, a clear cause of the disease, which is schizophrenia, has not been defined. The interest in psychotic diseases maybe already noticed in the circles of ancient cultures, e.g., in Vedas of ancient Hindus or Babylonian documents[i]. However, one of the first scientists who characterised the disease professionally was legendary Emil Kraepelin. It was he who arranged psychotic disorders into two groups: dementia praecox and manic–depressive insanity [2]. Currently, among modern scientists, the new trend of rediscovering the idea of schizophrenia as dementia praecox is noticeable. This is confirmed by the fact that cognitive damage criteria were included in the diagnostic criteria of schizophrenia in the newest version of ICD [3].« Re-Kraepelinization » and thus come back to the concept of premature dementia emphasizes on cognitive disintegration. Therefore it reminds us about the biological character of this illness.

Stress and diathesis model of schizophrenia

As aforementioned, the exact etiology of schizophrenia is not known, although several factors might come into play. In a meta-analysis of genome-wide association studies, over 100 loci related to its pathogenesis were discovered that are related to dopamine synthesis and receptors, which are a common target for antipsychotics, immunology, such as MHC complex,

which might be linked to abnormal synaptic pruning, and glutamatergic transmission [4,5,6]. The genetic abnormalities explain the etiology of schizophrenia only partially, which suggests significant environmental or epigenetic factors present in its development. This relationship between innate factors and subsequent life events forms the stress and diathesis model of schizophrenia's etiology.

According to this theory, mutations in said loci create an increased risk of developing this disorder, yet are not always sufficient for it to occur. There are many other factors related both to the pre-and postnatal life of a subject. Said factors are pre-and perinatal events such as infections in utero, preeclampsia in mother, low birth mass or using forceps during birth and urbanity, migration, chronic and acute stress, adverse events, social isolation, and substance use in further life [4,5]. Such events disrupt the normal development of synapses in CNS [4], lead to prolonged activation of HPA axis, imbalances in endocannabinoid and glutamatergic systems and finally - to dopamine dysregulation and psychosis [4].

Role of neurotransmitters in schizophrenia

Dysregulation of neurotransmitters is considered to be the primary mechanism of psychotic changes characteristic of schizophrenia recently. The dopamine hypothesis was first considered and is of crucial importance to this day. Initially, it was argued that the cause of psychotic disorders is a simple overactivity of the dopaminergic system. This was because agonists like amphetamines caused schizophrenic-like symptoms and on the other hand, first antagonists like chlorpromazine or haloperidol helped to cure delusions [7]. Over time, functional dissimilarities of the dopamine receptors were discovered, especially between D1- and D2- receptors. Thus, the dopamine theory began to evolve coupled with the knowledge of their location in the brain. Positive symptoms were associated with hyperactivation of D2-receptors in the ventral striatum and disruption of the cortical pathway passing through the nucleus accumbens. Negative symptoms were associated with D1-receptor insufficiency in the dorsolateral prefrontal cortex and decreased nucleus caudatus [8,9].

Interestingly, nicotine has a protective role against negative symptoms as it stimulates dopaminergic transmission [10]. The beneficial fact is that the D2-receptor level in the prefrontal cortex is low, and D2-antagonist drugs do not contribute significantly to the negative symptoms. However, these drugs reduce the effect of dopamine, inhibiting the secretion of prolactin in the tubero-fundibular pathway, which is the cause of hyperprolactinemia.

Recent neuroimaging studies (measured with positron emission tomography as the uptake of [18] DOPA) suggest that this is an increase in dopamine in the dorsal/associative striatum. In contrast, the dopamine concentration in the ventral striatum is normal to decrease [11].

Another essential concept is the serotonin hypothesis. Attention was drawn to the psychomimetic effect of serotonin-like substances in the 1960s thanks to LSD, a 5-HT agonist [12]. Meanwhile, the distribution of 5-HT2A receptors in the frontal cortex of patients with schizophrenia was only recently investigated in more detail in postmortem receptor studies. Atypical antipsychotics, the first of which was clozapine, have extended their spectrum of action to include antagonism 5-HT2A. While classic neuroleptics mainly helped in the treatment of productive symptoms, atypical drugs also had a positive effect on negative symptoms. The mechanism of action of these drugs is twofold. Serotonin antagonism reduces the "kindling" of dopaminergic and glutamatergic neurons and, as a result, reduces the release of dopamine in the nucleus accumbens, which has an antipsychotic effect. Besides, the blockade of serotonin receptors in the mesocortical pathway increases dopamine secretion in the prefrontal cortex. Unfortunately, 5-HT2A-antagonists activate dopaminergic neurons in the striatum, which contributes to extrapyramidal symptoms as a side effect [13].

The additional mechanism was investigated due to observing the psychomimetic action of phencyclidine (PCP), an antagonist of glutamate receptors (NMDAR). Moreover, negative symptoms were observed in healthy subjects in ketamine (also NMDAR antagonist) research [14]. Hypofunction of the NMDA-receptor, possibly on critical GABAergic interneurons, may indirectly affect dysregulation of dopaminergic transmission in important regions such as the prefrontal cortex and the hippocampus [15]. An example of such a disorder is antiNMDAR-encephalitis, in which the antagonist role is played by antibodies G, and the spectacular course resembles schizophrenia [16]. In summary, NMDA receptors may become the target of effective drugs for schizophrenia in the future. Preliminary reports with glycine modulators show promising but uncertain results [17].

Finally, it should be emphasized that nowadays, the pathogenesis of schizophrenia is perceived as a broad spectrum of neurotransmitter disorders. Therefore, the individual pathways interact with each other and cannot be treated selectively. On the other hand, the correlation of these disorders with the disease phenotype should be investigated, which may benefit from individualized treatment.

The interplay between internistic vulnerabilities and external stressors is the key to

understanding the pathogenesis of schizophrenia. However, there is a growing body of evidence suggesting novel mediators, such as microglia, the primary immune cells of the central nervous system. Recent advances suggest the critical role of variations of the complement system for the overactivation of microglia in people with schizophrenia. This can lead to loss of grey matter and cognitive and negative symptoms and accounts for several changes in the functional and structural changes observed within this disorder.

Activated microglia- two basic states

The activated microglial cells appear in two basic states, characterised as M1 and M2. The first pathway is triggered by IFN-G, IL-1B and TNF-a, and is typically induced by neuronal damage. Within this state, cells release proinflammatory compounds, NO, IL-1B, TNF-a, IL-6 and glutamate. It is followed by a shift to the latter state. Cytokines like IL-4, IL-13, and IL-25 trigger this shift. It is to observe that in this state, microglia cells facilitate anti-inflammatory response. It is endorsed by the release of compounds like IL-10, IGF-1, TGF-B and various neurotrophic factors. Given these ability the M2 pathway is involved in debris clearance, extracellular matrix deposition, and angiogenesis [18]. There is a growing body of evidence that dominance of the M1 pathway in adolescents is followed by sensory gating deficits in adulthood [19].

Role of microglia

The role that microglia plays in the functioning of CNS is yet to be fully established. Certainly, activation of the microglia leads to the survival of neurons [20] and phagocytose of the neural precursor cells. However, lack of activation leads to deficits in synaptic pruning and connectivity [21], overactivation causes excessive synaptic loss [22].

Stress and microglia

Stressful events, especially in the perinatal period, may lead to changes in microglia's functioning and structure. Ionized calcium-binding adaptor molecule 1 (IBA-1) expression is a marker of its density. Its levels are increased in footshock, restraint, social defeat, maternal

separation, and social isolation. Moreover, glucocorticoid receptor agonists cause proinflammatory changes in microglia [23]. However, perinatal stress leads to blunted CS response in adulthood [24] but increases the density of microglia [25,26]. Thus, it may trigger the priming leading to the overactivation of microglia in adulthood of rats exposed to perinatal stressors [27].

Perinatal stressors are widely known factors of developing structural and functional changes in developing organisms. Humans show a unique feature of late synaptic remodeling that remains active until early adulthood. It is still unclear how long is the crucial period for changes in microglia density. However, it is clear that it ends in the early postnatal period [28]. This time, which is characterised by extensive neuronal remodeling, is also the time of exceptional vulnerability. Activation of microglia in the perinatal period primes are kindling - exaggerated response to abnormally subtle stimuli in adulthood [29].

Schizophrenia and microglia

The structure and functioning of microglia are intensively researched. Radioligands binding to the translocator protein (TSPO) have been used to assess in vivo alternations in microglia in patients with schizophrenia. The developments suggest increased binding potentials in a whole-brain gray matter [30] and hippocampus [31]. In addition, several studies have found associations between the magnitude of ligand binding and symptom severity [32,33].

Other studies have shown that people with schizophrenia present increased microglia density, activation, and degeneration compared to controls [34,35]. Moreover, there is a growing body of evidence that antipsychotics cause dampening of microglial activity [36].
The dichotomy between M1 and M2 activation pathways of microglia cells appears to play a crucial role in the damages caused to the central nervous system. The cytokines levels can distinguish particular pathways. For example, proinflammatory cytokines levels are higher among individuals presenting symptoms of schizophrenia [37]. They also lead to reductions in hippocampal and prefrontal cortex volumes [38,39].

The meaning of complement system activation for the pathogenesis of schizophrenia is yet to be fully uncovered. A genome-wide genetic association study identified 100 loci associated with schizophrenia. One of them implicated the complement component 4.

It generates more C4 and therefore promotes attaching C3 to the synapse, leading to the neural cell's phagocytosis [40].

As aforementioned, the schizophrenic process is linked to various abnormalities in the function of the immune system. Activation of microglia and lymphocyte infiltration has severe consequences in relation to the physiology of brain tissue on a molecular level. This disturbance leads to changes in the metabolism of neurotransmitters and their precursors (i.e., increased activity of IDO) and the presence of compounds such as kynurenic acid being the result of ongoing inflammation [6,41]. Such changes in the biochemistry of cerebral tissue might be the factor leading to both psychiatric symptoms of schizophrenia and changes in CNS morphology [42].

An important and relatively well-studied aspect of the neuroimmunological abnormalities present in schizophrenia is the glutamatergic imbalance related to exaggerated and prolonged activation of microglia. Characterised before, the M1 response of activated microglia, focused mainly on IL1-B, TNFa, IL6, IFNg, NO, and glutamate secretion, is a proinflammatory mechanism frequently triggered by neuronal injury. The over-abundance of glutamate, activating its excitatory receptors and thus excitotoxicity [6,43] paired with reactive oxygen species present as the result of neuroinflammation, leads to synaptic loss and neuronal damage death [6,43]. It is also hypothesised that the NMDAR hypofunction in GABAergic interneurons leads to the reduced activity which causes disinhibition of cortical glutamatergic transmission, responsible for positive symptoms during acute psychosis. On the other hand, the decrease of said transmission can explain the negative symptoms of schizophrenia. Lower levels of glutamate, glutamine can support it, and glutathione is observed in MR spectroscopy in patients with schizophrenia [43].

The ongoing inflammation does not only tilt the balance of glutamatergic transmission in the brain by release of glutamate [6], or disinhibition of cortical glutamatergic interneurons [43]. This state promotes the induction of Indoleamine-pyrrole 2, 3-dioxygenase (IDO). This enzyme breaks down tryptophan into neuroactive compounds such as kynurenic acid and quinolinic acid. Also, other neurotransmissions dopaminergic, noradrenergic and aforementioned GABAergic, appear to be affected by metabolites of this pathway. Moreover, upregulation of IDO leads to serotonin depletion and depressive symptoms [41].

Apart from inflammation-related changes in adults' CNS occurring in schizophrenia, the role of proinflammatory cytokines - mainly IL1B and IL-6 appears to be important in the

developmental aspect of said disorder. The first of them is shown to induce dopaminergic phenotype in rats' mesencephalic progenitor cells, while the latter decreases the survival of serotonergic neurons in fetal brains [44]. Furthermore, the increased role of microglia in synaptic pruning [21,22] might lead to cortical dysregulation via excessive synaptic loss in PFC and hippocampus, which can be a viable explanation of lower grey matter volume in said areas and cognitive decrease and negative symptoms. Said symptoms and volume loss are observed to be correlated. Disrupted cortical development can be also responsive for the disinhibition of subcortical dopaminergic neurons, which might underlie positive symptoms [41].

Role of microbiome

The gut microbiome dysregulation is observed in many systemic diseases, even well-described for depression. So it may not be surprising that in some clinical studies, dysbiosis is also implicated in schizophrenia. It is worth noting that they were already shown during the first episode of psychosis. Moreover, microbiota imbalance is directly related to the increased permeability of the intestinal mucosa to various substances. They include inflammatory cytokines (IL-1beta, IL-6, TNF-alpha) that stimulate the HPA axis and microglia. On the other hand, short-chain fatty acids (SCFAs) formed in the physiological bacterial fermentation processes of undigested carbohydrates reduce the proinflammatory activity of microglia. Additionally, SCFAs affect adipocyte receptors, inhibit lipolysis, and reduce free fatty acids, which promotes weight normalization. Thus, a deficiency of good bacteria can enhance weight gain during antipsychotic treatment. In parallel, some microorganisms can produce neurotransmitters such as dopamine (e.g., *Bacillus, Proteus vulgaris, Serratia marcescens*) and serotonin (e.g., *Candida, E. coli, Enterococcus*) which act on vagus nerve and enteric nervous system. Moreover, antibodies to the fungus *Saccharomyces* cerevisiae (ASCA) were statistically more common in patients with schizophrenia. However, what is interesting, paradoxically, Proteobacteria and Firmicutes were found both significantly elevated and reduced in schizophrenia. Perhaps the one genuinely consistent conclusion is a significant elevation of Lactobacilli in schizophrenia, and what is more, it even correlates with symptom severity. Though it may seem perplexing, considering that Lactobacilli are standard components of probiotics. Thought to be beneficial for mental health, it does have a probable, reasonable explanation – it depends on which specific subtype of Lactobacilli is present in the patient's gastrointestinal system and can be related to both the pathogenesis of psychiatric

disorders bring benefits to them [45]. Prebiotics (mainly non-digestible oligosaccharides which are utilized by host microorganisms) in rodent studies enhanced glutaminergic transmission in the prefrontal cortex and increased BDNF levels in the hippocampus. Such changes would have a positive effect on cognitive impairment in patients with schizophrenia. However, preliminary studies claim that supplementation by probiotics (*Lactobacilli* and *Bifidobacteria*) does not improve the PANSS score. However, probiotics reduce the constipation problem often caused by antipsychotic treatment [46].

Conclusions

As discussed above, the pathogenesis of schizophrenia is a complex topic. This disorder appears to be caused by dysregulation of transmission between various parts of the brain with ongoing inflammatory processes (i.e., microglial activation, lymphocyte infiltration, elevated cytokines) linked to environmental (past infections, urbanity, psychological) trauma) and genetic factors. What is sure is that current data do not provide evidence for the existence of a single deciding factor.

Schizophrenia is a problem both for individual patients and the healthcare system as the affected frequently lose their ability to function in society independently. Furthermore, medications used to treat this disorder have worrisome side effects that can lower patients' compliance and lead to costly treatment situations. Despite best efforts, a significant percentage of people affected by schizophrenia do not achieve sufficient results after beginning the treatment, significantly when alleviating negative symptoms.

The complexity of changes occurring in physiology and anatomy of the central nervous system of people who have schizophrenia, however daunting, may present a chance of developing a new line of treatment focused, for example, more on mitigating the immunological disturbances than imbalances in neurotransmitters. As it is currently studied, the link between immunology and psychiatric disorders seems more potent than it was thought before.

References

1. Mednick S.A., Cannon T.D., Barr C.E., & LaFosse J.M. (Eds.): Developmental neuropathology of schizophrenia. Nato Science Series A, 1991, 217, 93-120.

2. Adityanjee, Aderibigbe Y.A., Theodoridis, D. and Vieweg, W.V.R.: Dementia praecox to schizophrenia: The first 100 years. Psychiatry and Clinical Neurosciences, 1999, 53, 437-448.
3. Sampogna G.: ICD-11 – Draft diagnostic guidelines for mental disorders: A report for WPA Membership, WHO Collaborating Center for Research and Training in Mental Health. Psychiatria Polska, 2017, 51(3), 397–406.
4. Valle R.: Schizophrenia in ICD-11: Comparison of ICD-10 and DSM-5. Revista de Psiquiatría y Salud Mental (English Edition), 2020, 13(2), 95-104.
5. Stilo S.A., Murray R.M.: Non-Genetic Factors in Schizophrenia. Current psychiatry reports, 2019, 21(10), 100.
6. Howes O.D., & McCutcheon R.: Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization. Translational psychiatry, 2017, 7(2), e1024.
7. Carlsson A.: The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology, 1988, 1(3), 179–186.
8. Shen L.H., Liao M.H., Tseng Y.C.: Recent advances in imaging of dopaminergic neurons for evaluation of neuropsychiatric disorders. Journal of Biomedicine and Biotechnology, 2012, 1-14.
9. O'Donnell P., & Grace A.A.: Dysfunctions in multiple interrelated systems as the neurobiological bases of schizophrenic symptom clusters. Schizophrenia Bulletin, 1998, 24(2), 267-283.
10. Luckhaus C., Henning U., Ferrea S., Musso F., Mobascher A., Winterer G.: Nicotinic acetylcholine receptor expression on B-lymphoblasts of healthy versus schizophrenic subjects stratified for smoking: [3 H]-nicotine binding is decreased in schizophrenia and correlates with negative symptoms. Journal of neural transmission, 2012, 119(5), 587-595.
11. Kegeles L.S., Abi-Dargham A., Frankle W.G., Gil R., Cooper T B., Slifstein M., Laruelle M.: Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Archives of General Psychiatry, 2010, 67(3), 231–239.
12. De Gregorio D., Comai S., Posa L., Gobbi G.: D-Lysergic Acid Diethylamide (LSD) as a model of psychosis: Mechanism of action and pharmacology. International Journal of Molecular Sciences, 2016, 17(11), 1953.

13. Steeds H., Carhart-Harris R.L., Stone J.M.: Drug models of schizophrenia. Therapeutic Advances in Psychopharmacology, 2015, 5(1), 43–58.
14. Thiebes S., Leicht G., Curic S., Steinmann S., Polomac N., Andreou C., Mulert C.: Glutamatergic deficit and schizophrenia-like negative symptoms: new evidence from ketamine-induced mismatch negativity alterations in healthy male humans. Journal of Psychiatry & Neuroscience, 2017, 42(4), 273–283.
15. Coyle J.T.: Glutamate and schizophrenia: beyond the dopamine hypothesis. Cellular and Molecular Neurobiology, 2006, 26(4–6), 365–384.
16. Teixeira A.L., Rocha N.P., Zhang X.: Anti-NMDAR antibodies as a new piece in schizophrenia's puzzle. Future Science, 2017, 3(2), 178.
17. de Bartolomeis A., Manchia M., Marmo F., Vellucci L., Iasevoli F., Barone A. . Glycine signaling in the framework of dopamine-glutamate interaction and postsynaptic density. Implications for treatment-resistant schizophrenia. Frontiers in Psychiatry, 2020, 11, 369.
18. Cherry J.D., Olschowka J.A. & O'Banion M.K.: Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. Journal of Neuroinflammation. 2014, 11, 98.
19. Eßlinger M., Wachholz S., Manitz M. P., Plümper J., Sommer R., Juckel G., & Friebe A.: Schizophrenia associated sensory gating deficits develop after adolescent microglia activation. Brain, behavior, and immunity, 2016, 58, 99–106.
20. Ueno M., Fujita Y., Tanaka T., Nakamura Y., Kikuta J., Ishii M., Yamashita T.: Layer V cortical neurons require microglial support for survival during postnatal development. Nature Neurosci, 2013, 16(5), 543-51.
21. Paolicelli R.C., Bolasco G., Pagani F., Maggi L., Scianni M., Panzanelli P., Giustetto M., Ferreira T.A., Guiducci E., Dumas L., Ragozzino D., & Gross C.T.: Synaptic pruning by microglia is necessary for normal brain development. Science (New York, N.Y.), 2011, 333(6048), 1456–1458.
22. Hong S., Beja-Glasser V.F., Nfonoyim B.M., Frouin A., Li S., Ramakrishnan S., Merry K.M., Shi Q., Rosenthal A., Barres B.A., Lemere C.A., Selkoe D.J., Stevens B.: Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science, 2016, 6, 352(6286), 712-716.
23. Frank M.G., Thompson B.M., Watkins L.R., & Maier S.F.: Glucocorticoids mediate stress-induced priming of microglial proinflammatory responses. Brain, behavior, and immunity, 2012, 26(2), 337–345.

24. Bilbo S.D., Yirmiya R., Amat J., Paul E.D., Watkins L.R., Maier S.F.: Bacterial infection early in life protects against stressor-induced depressive-like symptoms in adult rats. Psychoneuroendocrinology, 2008, 33(3), 261-269.
25. Hagberg H., Mallard C., Ferriero D.M., Vannucci S.J., Levison S.W., Vexler Z.S., & Gressens P.: The role of inflammation in perinatal brain injury. Nature reviews. Neurology, 2015, 11(4), 192–208.
26. Sominsky L., Walker A.K., Ong L.K., Tynan R.J., Walker F.R., & Hodgson, D.M.: Increased microglial activation in the rat brain following neonatal exposure to a bacterial mimetic. Behavioural brain research, 2012, 226(1), 351–356.
27. Diz-Chaves Y., Pernía O., Carrero P., & Garcia-Segura L.M.: Prenatal stress causes alterations in the morphology of microglia and the inflammatory response of the hippocampus of adult female mice. Journal of neuroinflammation, 2012, 9, 71.
28. Manitz M.P., Esslinger M., Wachholz S., Plümper J., Friebe A., Juckel G., & Wolf R.: The role of microglia during life span in neuropsychiatric disease--an animal study. Schizophrenia research, 2013, 143(1), 221–222.
29. Gogtay N., Vyas N.S., Testa R., Wood S. J., & Pantelis C.: Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophrenia bulletin, 2011, 37(3), 504–513.
30. van Berckel B.N., Bossong M.G., Boellaard R., Kloet R., Schuitemaker A., Caspers E., Luurtsema G., Windhorst A.D., Cahn W., Lammertsma A.A., & Kahn R.S.: Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biological psychiatry, 2008, 64(9), 820–822.
31. Doorduin J., de Vries E F., Willemsen A. T., de Groot J.C., Dierckx R.A., & Klein H C.: Neuroinflammation in schizophrenia-related psychosis: a PET study. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 2009, 50(11), 1801–1807.
32. Bloomfield P.S., Selvaraj S., Veronese M., Rizzo G., Bertoldo A., Owen D.R., Bloomfield M.A., Bonoldi I., Kalk N., Turkheimer F., McGuire P., de Paola V., & Howes O.D.: Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [(11)C]PBR28 PET Brain Imaging Study. The American journal of psychiatry, 2016, 173(1), 44–52.
33. Takano A., Arakawa R., Ito H., Tateno A., Takahashi H., Matsumoto R., Okubo Y., Suhara T.: Peripheral benzodiazepine receptors in patients with chronic schizophrenia:

a PET study with [11C]DAA1106. The international journal of neuropsycho-pharmacology, 2010, 13(7), 943–950.

34. Hercher C., Chopra V., & Beasley C.L.: Evidence for morphological alterations in prefrontal white matter glia in schizophrenia and bipolar disorder. Journal of psychiatry & neuroscience, 2013, 39(6), 376–385.
35. Fillman S.G., Cloonan N., Catts V.S., Miller L.C., Wong J., McCrossin T., Cairns M., & Weickert C.S.: Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Molecular psychiatry, 2013, 18(2), 206–214.
36. Zhu F., Zheng Y., Ding Y.Q., Liu Y., Zhang X., Wu R., Guo X., & Zhao J.: Minocycline and risperidone prevent microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of lipopolysaccharide in rats. PloS one, 2014, 9(4), e93966.
37. Goldsmith D.R., Rapaport M.H., & Miller B.J.: A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Molecular psychiatry, 2016, 21(12), 1696–1709.
38. Cannon T.D., Chung Y., HeG., Sun D., Jacobson A., van Erp T.G., McEwen S., Addington J., Bearden C.E., Cadenhead K., Cornblatt B., Mathalon D. H., McGlashan T., Perkins D., Jeffries C., Seidman L.J., Tsuang M., Walker E., Woods S. W., Heinsse, R.: North American Prodrome Longitudinal Study Consortium. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biological psychiatry, 2015, 77(2), 147–157.
39. Mondelli V., Cattaneo A., Murri M.B., Di Forti M., Handley R., Hepgul N., Miorelli A., Navari S., Papadopoulos A.S., Aitchison K.J., Morgan C., Murray R.M., Dazzan P., & Pariante C.M.: Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. The Journal of clinical psychiatry, 2011, 72(12), 1677–1684.
40. Sekar A., Bialas A.R., de Rivera H., Davis A., Hammond T.R., Kamitaki N., Tooley K., Presumey J., Baum M., Van Doren V., Genovese G., Rose S. A., Handsaker R.E.: Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly M.J., Carroll M.C., Stevens B., & McCarroll S.A. Schizophrenia risk from complex variation of complement component 4. Nature, 2016, 530(7589), 177–183.

41. Wang Q., Liu D., Song P., & Zou M.H.: Tryptophan-kynurenine pathway is dysregulated in inflammation, and immune activation. Frontiers in bioscience (Landmark edition), 2015, 20, 1116–1143.
42. Laskaris L.E., Di Biase M.A., Everall I., Chana G., Christopoulos A., Skafidas E., Cropley V.L., & Pantelis C.: Microglial activation and progressive brain changes in schizophrenia. British journal of pharmacology, 2016, 173(4), 666–680.
43. Kumar J., Liddle E.B., Fernandes C.C., Palaniyappan L., Hall E.L., Robson S.E., Simmonite M., Fiesal J., Katshu M. Z., Qureshi A., Skelton M., Christodoulou N.G., Brookes M.J., Morris P.G., & Liddle P.F.: Glutathione and glutamate in schizophrenia: a 7T MRS study. Molecular psychiatry, 2020, 25(4), 873–882.
44. Müller N.: Inflammation in Schizophrenia: Pathogenetic Aspects and Therapeutic Considerations. Schizophrenia bulletin, 2018, 44(5), 973–982.
45. Misiak B., Łoniewski I., Marlicz W., Frydecka D., Szulc A., Rudzki L., & Samochowiec, J.: The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2020, 102, 109951.
46. Szeligowski T., Yun A.L., Lennox B.R., Burnet P.W.J.: The gut microbiome and schizophrenia: The current state of the field and clinical applications. Frontiers in Psychiatry, 2020, 11, 156.

VARIA

Opinions of Internet users regarding experiments conducted on animals

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Introduction

Since antiquity, animal experiments have served scientific purposes, mainly learning anatomy, physiology, and other branches of medicine. Aristotle, the author of "On Parts of Animals", conducted dissections on dead animals [1]. The first vivisection on the animal is credited to Andreas Vesalius (1514-1594). For many years, however, this procedure, like others, was performed without any anesthesia because scientists ignored the fact of inflicting pain on animals, explaining it most often by their inability to feel suffering

In the 17th century, vivisections were criticized due to the emergence of the view that suffering interferes with the functioning of the body's organs, and therefore experiments do not bring reliable results. Only in the nineteenth century, with the emergence of humanistic trends, perceiving the suffering of animals, animals subjected to the procedures were previously anesthetized. At the same time, the anti-revision movement began to develop. Britain passed The Cruel Treatment of Cattle Act (1822), prohibiting the cruel treatment of pets, and the Cruelty to Animals Act (1876), the first law to regulate animal experimentation. Today, guided by the availability of other alternative methods and their greater credibility and moral reasons, more and more scientific institutions are trying to reduce the amount of research carried out on animals [1].

In the 60’s of the 20th century [2] social protetsts began on exploiting animals in the USA. A breakthrough highlighted in the literature on the subject was the publication by Peter Singer, "Animal Liberation," in which the author (an ethicist and philosopher) looked at how

animals were treated by humans, primarily to provide substantive arguments people fighting for animal rights.

Despite many controversies, an important role in the development of medical sciences is played by laboratory animals. Experiments with the use of animals constitute the initial stage of drug research, preceding clinical trials in which substances come into contact with the human body [3]. Such experiments are always carried out in special rooms and with the Ethics Committee for Animal Experiments [4]. Animal studies are not randomized trials and the organisms involved are not random. Their source must be places intended for breeding, the owners of which have special permissions for the experiments, mice, rats, voles, guinea pigs, gerbils, rabbits, dogs, cats, and other mammals [4].

In 2004, the European Union banned testing cosmetics on animals [5]. On March 11, 2013, a complete ban on the use of ingredients in cosmetic products that had been tested on animals was introduced, and the marketing of products containing such ingredients was prohibited. Cosmetics are the only product group that has been banned [6].

In Poland, in 2019, according to data published on www.bip.nauka.gov.pl, animals were used for scientific experiments [7]. One goal of animal research is to expand knowledge on the prevention, diagnosis, and treatment of diseases and develop broadly understood pharmacotherapy. Toxicological tests are also considered essential as Sakowski [8], i.e., checking the doses in which certain substances are dangerous and lethal, which, for obvious reasons, cannot be tested on humans. Such tests determine the LD50 parameter, or dose, based on the number of milligrams of a given compound per kilogram of body weight that will kill half the population.

Another very important reason is the widely understood medicine and medical biology and dietetics and nutritional research (testing drugs, new techniques, e.g., surgery, and the long-term influence of particular chemical compounds in food on health) [6].

However, performing experiments with the use of animals still raises a lot of controversies, is the subject of clashes between supporters and opponents of this type of activity [9-13].

On the one hand, there are opinions of researchers who firmly point out that the prohibition of conducting research and experiments on animals may lead to stagnation in science, and on the other. There are more and more voices of opposition to similar actions, that man has no right to cause specific harm to other living creatures.

Therefore, we decided to get to know the opinions of Internet users regarding experiments with animals.

Material and methods

The study was carried out in November 2020-February 2021, using the diagnostic survey in a group of 622 Internet users by disseminating the own-authored questionnaire via the online platform (survio.com; google.pl) distributed using the snowball technique.

The obtained material was analyzed and developed using the basic descriptive statistics with the use of MS Excel.

This study included (72% women and 174 28% men aged 17-75 (mean age 31.4 ± 10.5). More than half (52%) of the group were people under 40 years of age.

Almost 40% were school pupils/students; 34.7% were professionally active white-collar workers; 19.0% - professionally active blue-collar workers; 8.7% were retirees and 3.9% - professionally inactive people. City residents accounted for 74% and village residents 26%.

Results

The vast majority of respondents (86.5%) had a pet. Sixty-six percent had a dog, and 56% had more than one pet. Forty-two percent had animals for more than two years. Forty-two percent had a cat, parrot (18%), hamster (16%), guinea pig (11%), rabbit (9%), rats and chinchillas (4% each), and canary (3%) owners.

As many as 67.1% declared that they treat their pet as a full-fledged family member.

The respondents were questioned if the man who owns the animals can do whatever he wants with him, without any restrictions. The vast majority of the respondents (97.1%) gave a negative answer.

The respondents were also asked to determine whether animals could be killed in certain circumstances. The respondents would most often allow killing animals when they were very sick, tired, and could no longer be helped (49.8%) and when they were to be used for meat or other economic needs (35.4%). The answers are presented in Table I.

Another question was related to the opinion on punishing people for inappropriate behavior towards animals. Almost all (98.4%) respondents favored severe punishment in the case of abuse of an animal, their own or stray and killing unnecessarily, for fun (94.5%). The vast majority of respondents (90.4%) had negative opinions on testing cosmetic or therapeutic agents on animals in a way that causes them suffering. Details are presented in Table II.

Table I. Circumstances are justifying, according to the respondents, killing animals.

Answer	Yes	No	It is difficult to say
For meat or other economic needs	35.4%	24.1%	40.5%
They are very sick, they get tired and cannot be helped	49.8%	16.1%	34.1%
They are dangerous and dangerous to humans	21.5%	44.4%	34.1%
They are harmful	16.4%	53.1%	30.5%
They are useless	1.3%	87.8%	10.9%
All without any special restrictions	0	94.5%	5.5%

Table II. Respondents opinions on punishing people for inappropriate behavior towards animals

Answer	Punish severely	Punish mildly	Do not punish	I do not care	I do not know
They kill animals unnecessarily for fun	94.5%	4.4%	0	0	1.1 %
They bully an animal - their own or a stray animal	98.4%	1.6%	0	0	0
They transport animals, farm and slaughter, without providing them with food and water for many days	93.2%	5.8%	0	0	1.0%
They throw a dog or cat out of the house	86.8%	10.6%	0.3%	0.6%	1.7%
They compel animals to play, sport, or profit, behavior that may be painful for them	85.2%	12.9%	0.6%	0.6%	0.7%
They test the effects of cosmetic/ therapeutic agents on animals in a way that causes them suffering	90.4%	6.1%	1.0%	0.3%	2.2%
They keep animals in inappropriate living conditions, which is harmful to them and causes them to suffer	89.2%	10.3%	0.3%	0	0.2%
They don't heal sick animals	74%	19.3%	2.9%	0.3%	3.5%
They deal with animals in a malicious way, e.g. frighten them, irritate them, bind them for fun	83%	15.4%	1.0%	0.3%	0.6%
They violently feed livestock for slaughter, causing them to suffer in order to obtain adequate meat	88.1%	7.7%	1.3%	0.3%	2.6%
When breeding animals, they do not care about their possible damage and injuries	85.2%	12.2%	1.3%	0.6%	0.7%
They kill slaughter animals without prior proper stunning	88.7%	5.8%	1.6%	1.3%	2.6%
They make animals work beyond their strength	88.7%	6.8%	1.3%	0.6%	2.6%

The vast majority (92.6%) of surveyed have heard about the use of animals for experimental purposes. The most common areas in which animal experiments are carried out were indicated medicine (80.7%) and testing of cosmetics, detergents, and cleaning agents (66.9%).

Animal experiments were identified by Internet users, mainly with laboratory animals. Eighty-five percent of respondents indicated mice as the most frequently used animals, and 70.1% - rabbits.

An interesting issue was the public's opinion about whether the experiments were conducted humanly. The vast majority (80%) of the respondents, stated that they did not.

More than 1/3 (34.1%) of the surveyed reported that the laboratory animals' conditions are not appropriate.

The expression of concern and humanitarian approach should be, above all, the relief of pain associated with the performed experiment. However, the perception of pain by animals of particular species is a controversial issue. The vast majority (88.4%) of respondents reported that all animals feel pain in the same way as humans.

One of the areas in which animal experiments are used is the development of science, including biology and medical sciences. An alternative to conducting experiments on animals in universities and schools, in which an animal is killed or painful for scientific purposes, could be the use of modern technologies, including virtual reality. Most of the respondents (71.7%) indicated that experiments that could be replaced with the use of a computer should be prohibited. Details are summarised in Table III.

The opinions of the respondents on the safety of products tested on animals were also analysed. Only 19% were convinced that they were safe, and 42.4% had no opinion on this matter.

The fact that animal experiments are complicated and painful, mainly for animal lovers, was convinced by 62.9% of the respondents.

The next question in the questionnaire concerned the impact of experiments with animals on humans. The vast majority stated that such incidents increase a person's sense of power and superiority over others (68.8%). More than half of respondents (58.8%) reported that the experiments had a destructive effect on the mind and emotions of a person who participates in such research. Less than half (40.5%) of the respondents indicated that the animals participated in experiments influencing the development of medicine, transplantology, genetics, and pharmacy.

Table III. Opinions of the respondents on selected aspects related to the conduct of experiments

Answer	Definitely yes	Yes	It is difficult to say	No	Definitely not
The experiments cause pain and suffering to animals	62.7%	18.0%	16.7%	1.0%	1.6%
The experiments cause stress	72.7%	17.7%	7.7%	1.6%	0.3%
They are the cause of great fear	69.5%	19.9%	7.4%	2.6%	0.6%
They cause permanent damage to the organism of animals	59.2%	21.2%	18.3%	1.0%	1.3%
They take place in a human manner	5.8%	7.1%	37.6%	21.2%	28.3%
Optimum conditions are ensured	5.8%	9.3%	39.9%	18.3%	26.7%

The final questions included in the questionnaire related to legal regulations. Less of half (45.3%) of the surveyed had no idea about it.

Discussion

The aim of this study was to find out the opinions of Internet users regarding experiments with animals. In the present study, we found that most respondents have heard about the use of animals for experimental purposes and believed that the conditions they are staying in and the experiments are not appropriate. Most respondents thought experiments with animals increased humans' sense of power and superiority over others, aggression, and higher feelings' disappearance. Most surveyed were convinced that animal experiments caused them pain and caused suffering, stress, and fear and should be strictly forbidden. Our findings are similar to reports on attitudes toward animal experiments. In a study from Georgia [14] was explored public attitudes towards animal research. Totally 750 interviews were conducted. For most respondents (68.0%), animal use in Biomedical research is acceptable. And 82.0% of respondents fully or partly agreed with the concept that the involvement of animals in experiments complies with the principles of international norms and is acceptable. Furthermore, the authors found the respondents' attitude towards animal testing in biomedical research is influenced by age, education, and occupation. Gender, place of residence, and experience with

having animals do not affect the respondent's attitudes. In a study from Canada [15] using a web-based survey was used to explore people's willingness to support the use of mice in chronic versus acute pain research. The majority of the participants opposed the use of mice for either chronic (68.3%) or acute (63.1%) pain research. The results of a survey published in 2014 by the Department for Business, Innovation, and Skills showed that a majority of the British public accept the use of animals in medical research 'where there is no alternative' [16]. Of the 969 respondents questioned, 68% agreed that they could accept the use of animals in research for medical purposes where there are no alternatives – such as using computer modeling or in vitro testing. Results also revealed that 60% accepted the use of animals in research to help our understanding of the human body and 64% accepted use to increase understanding of animal health, where no alternative exists. Around half agreed that animals should only be used in medical research into 'life-threatening or debilitating diseases. In 2014, TNS survey [17] researched a representative sample of 1,000 Polish residents; 48% of the respondents had a pet at home. Most Poles had a dog (83%), and 44% had a cat (44%). Similarly, in our study, 86.5% of the respondents had a pet, dogs (66%),

Due to their dependence on agriculture, farming, and animal husbandry, it is worth remembering that traditional societies had a strong relationship with animals treated as breadwinners and family members [18,19]. Similarly, in our research, 67.1% declared that they treat their pet as a full-fledged family member.

Unfortunately, the latest statistics from the Ministry of Justice, Poland, showed that the number of crimes against animals has increased. In 2004, there were over 990 crimes against animals, and in 2015 - 1,859 [20]. In the years 2012–2014, were 4,475 cases of crimes against animals. The most frequent victims of crime were domestic animals (65.7%), farm animals (32.6%), and wild and wild animals (1.7%) [21].

Almost all respondents (98.4%) from the current survey were in favor of severe punishment in bullying an animal and killing them unnecessarily. According to 94.5% of the respondents, no circumstances are justifying killing animals.

In our study, the ecological trend is observing, and greater sensitivity to the natural environment, including animals, was also reflected in the consumption of products and diet differentiation. Currently, most Internet users have limited meat products in their diet. The use of a meat-free diet, depending on the situation, was declared by 30.5% of respondents, a vegan diet was used by 6.1%, and 13.2% converted to vegetarianism, which is closely related to the elimination of animal products.

Experiments using different species of animals as research models are carried out in many scientific disciplines, such as medicine, pharmacy, dermatology, cosmetology, agriculture, and zootechnics. In the current study, the most common areas in which animal experiments are conducted were indicated as medicine (80.7%) and cosmetology, e.g., testing cosmetics and cleaning products (66.9%). Slightly less frequently, genetic and education studies were reported. A 2013 study on a representative random sample of 1,101 adult residents of Poland showed that 58% of respondents believed that it was right to test medicines for humans on animals, 30% - to test cosmetics and clean products. They were much more opposed to testing cosmetics on animals, cleaning products, and medicines, respondents under 25 years of age [18]. In the surveyed group of Internet users, the vast majority (92.6%) had heard about the use of animals for experimental purposes. As many as 90.4% were against testing the effects of cosmetic/therapeutic agents on animals in a way that caused them suffering. Although the majority of 2013 respondents were against testing cosmetics and cleaning products on animals, only 10% of them checked whether they were tested on them when they purchased them. Women (15%) paid more attention to whether cosmetics and cleaning products were tested on animals than men (5%) [18]. In our study, a much larger number of people (37.3%) paid particular attention to cruelty-free products - that is, not tested on animals and avoided them. The latest survey from 2020 by Cruelty-Free Europe showed that 80% of adults in Poland reported that the European Union should invest more in research methods alternatives to animal testing [19]. Also, nearly three-quarters (72%) of adults in EU member states agree that the EU should set binding targets and deadlines to phase out animal testing. Almost ¾ of the EU population believed that the EU should set binding targets and deadlines for a complete end to animal testing. A study conducted on the Ariadna panel in October 2019 on a nationwide group of 1,041 people over 18 years of age showed that 57% of surveyed Poles were against testing drugs on animals [20]. In a survey conducted by Savanta ComRes in June 2020, over 70% of respondents from 12 EU countries agreed that the EU should set binding targets and deadlines for a complete end to animal testing [19]. Respondents agreed that the EU should invest more in developing alternatives to animal testing, they agreed in Portugal - 85% of respondents, Croatia - 84%, Poland - 80%, Romania - 80%, Italy - 79 %, in Germany - 76% and in France - 75%. In a study from 2013, the majority (79%) of the Polish respondents reported that all animals feel pain in the same way as humans [21]. In the present study, 88.4% of respondents shared the opinion. On September 8, 2010, the European Parliament (EP) voted in favor of changes to the law on conducting experiments on animals, which have not been changed for 20

years [22]. The EP advocated a significant reduction in the use of animals in experiments. The use of animals for experiments is allowed only in strictly defined scientific experiments and in drug testing and species protection.

Guided by the experience from validation studies for alternative methods in toxicology, concepts of a Good Cell Culture Practice (GCCP) are currently being developed which aim to define minimum quality standards for in vitro techniques [23] .

During the last two decades, in vitro technology has been successfully developed and its use is continuously growing. Advanced tests avoiding animal experiments are required for routine industrial applications e.g. for pharmacological high-throughput screening [24].

In the current study, most respondents reported that it is necessary to verify and make appropriate changes in many precedents that fall victim to animals (limit the number of animals, better conditions for animals, ban commercial experiments and increase controls).

Conclusions

1. Most respondents have heard about the use of animals for experimental purposes and believe that the conditions they are held in and the experiments are inappropriate.
2. A majority also thought experiments with animals increased humans' sense of power and superiority over others, aggression, and decreased higher feelings.
3. Finally, most of those surveyed were convinced that animal experiments caused pain and suffering, stress, and fear and should be strictly forbidden.

References

1. Turlejewski K. Experimenting on animals. Myths, facts, needs, ethics and law. CARE Lecture, 2015. https://wszechnica.org.pl/ wyklad/ eksperymentowanie-na-zwierzetach-mity-fakty-potrzeby-etyka-i-prawo-wykład-care-prof-krzysztof-turlejski/, (cited 02.05. 2021)
2. Posłuszna E. Ecological extremism, . Wyd. Scholar, Warszawa, 2012.
3. Salińska E. Animal research as a driver of science, 2019, https://wszechnica.org.pl/ wyklad/badania-na-zwierzetach-jako-motor-nauki, (cited 02.05.2021)
4. Olszewski J., Jabłecka A., Piątek J., Samborski Wł., Zawadziński J. Pre-Clinical Experimental Studies On Animals, Nowiny Lekarskie, 2011, 80(3), 219–221.

5. Savanta: ComRes, 2020, https://comresglobal.com/polls/cruelty-free-europe-animal-tes-ting-in-the-eu/, (cited 02.05.2021).
6. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes Text with EEA relevance, http://data. europa.eu/eli/dir/2010/63/oj, (cited 02.05.2021)
7. Schollenberger A. The 3R principle in the protection of animals used for scientific purposes, Życie Weterynaryjne, 2017, 92(6), 424-426.
8. Sakowski Ł. Are animal experiments necessary? Substantive assessment without populism, 2019, https://www.totylkoteoria.pl/2019/07/eksperymenty-na-zwierzetach. html, (cited 02.05.2021)
9. Ranganatha N., Kuppast I.J. A review on alternatives to animals testing methods in drug development, International Journal of Pharmacy and Pharmaceutical Sciences, 2012, 5(4), 28-32.
10. Babińska I., Szarek J., Felsmann M. Z. et al. Animal experiments in historical perspective [in] Former medicine and veterinary medicine. Felsmann M. Z. Szarek J., Felsmann M. (ed.), Wyd. Rokpol Sp. z o.o., Chełmno, 2007: 235-241.
11. Babińska I., Szarek J., Felsmann M. Z., Kowalski I. M., Przeździecka D., Mieszczyński T. Evolution of Polish legal regulations for conducting experiments on animals [in:] Former medicine and veterinary medicine Felsmann M. Z. Szarek J., Felsmann M. (ed.), Wyd. Rokpol Sp. z o.o., Chełmno, 2007: 243-253.
12. Radecki W. Animal Protection Act – commentary. Wyd. Prawo Ochrony Środowiska, Wrocław, 2003.
13. Radecki W. Act: on animal protection, on animal experiments - with commentary. Wydawnictwo Delfin, Warszawa, 2007.
14. Melikishvili M., Mitskevich N., Pitskhelauri N., Lobzhanidze G., Chikhladze N.: Public Attitudes Towards The Use Of Animals In Biomedical Research In Georgia. Georgian Med News. 2018, 285, 130-134.
15. Ormandy E.H., Griffin G. Attitudes toward the use of animals in chronic versus acute pain research: results of a web-based forum. Alternatives *to* Laboratory Animals. 2016, 44(4), 323-335.
16. Public attitudes to animal testing. Public attitudes to animal testing - GOV.UK, 2014, www.gov.uk. (cited 02.05.2021)
17. Krassowska U. Animals in Polish homes, 2014, TNS, http://www.tnsglobal.pl/archiwu

mraportow/files/2014/11/K.073_Zwierz%C4%99ta_w_polskich_domach_O10a-14.pdf, (cited 02.05.2021)

18. Mamzer H. Posthumanism in contemporary family models: animals as family members? Oficyna Wydawnicza Arboretum, Wrocław, 2015.
19. Foer J.S. Eating animals, Penguin Books Ltd., 2011.
20. Report of the Ministry of Interior and Administration, https://www.polsatnews.pl/wiadomosc/2017-03-15/coraz-wiecej-przestepstw-przeciwko-zwierzetom-raport-mswiia/, 2017, (cited 02.05.2021).
21. Karaś D. How do Poles abuse animals? Report prepared by the Czarna Owca Pana Kota Foundation and the Ekostraż Animal Protection Association. Report on the monitoring of courts, prosecutor's offices and the police. Fundacja Czarna Owca Pana Kota, Kraków, 2016.
22. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, 2009, http://data.europa.eu/ eli/reg/2009/ 1223/oj, (cited 02.05.2021)
23. Gruber F.P., Hartung T. Alternatives to animal experimentation in basic research. ALTEX. 2004, 21(Suppl 1), 3-31.
24. Rozporządzenie Parlamentu Europejskiego i Rady (WE) nr 1223/2009 z dnia 30 listopada 2009 r. dotyczące produktów kosmetycznych, http://data.europa.eu/ eli/reg/2009/1223/oj, (cited pobrania 21.01.2021).

Accessibility and ethics in clinical trials

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Abberviations list

- AIDS - Acquired immunodeficiency syndrome
- AML - Acute myeloid leukaemia
- AHTATS - Agency for Health Technology Assessment and Tariff System
- CP - Centralized Procedure
- CLL - Chronic lymphoid leukaemia
- CTD - Common Technical Document
- DCP - Decentralized Procedure
- DLBCL - Diffuse large B-cell lymphoma
- EMA - European Medicines Agency
- EU - European Union
- GCP - Good Clinical Practice
- ICH - International Conference on Harmonization
- MCL - Mantle cell lymphoma
- M.D.S. - Myelodysplastic syndromes
- MM - Multiple myeloma
- MRP - Mutual Recognition Procedure
- NHF – National Health Fund
- ORMP - Office for Registration of Medicinal Products
- ORMPMDBP - Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
- OS – Overall Survival
- PSURs - Periodic Safety Update Reports
- SmPC - Summary of Product Characteristics

- TKI - tyrosine kinase inhibitor
- WHO - World Health Organization

Research ethics controversy

New drug clinical trials are essential for the introduction of new drugs to the market. Overall, the worldwide research ethics controversy has centered on three issues: the standard of care, the "reasonable availability; and the quality of informed consent [1]. This chapter focuses on the approach to the registration process and equality in advanced treatment availability. The history of clinical trials, the drug approval procedure, the rationale behind this complicated procedure, and its implications for patients with haematological malignancies are described.

History of clinical trials

Since the dawn of time, humanity has been trying to assess the safety of its treatment methods. The first document evaluated the efficacy and safety of drugs, usually of plant origin, thousands of years ago. An example of such attempts is described in the "Book of Daniel." The world's first clinical trial was not conducted by a medical, but by King Nebuchadnezzar. The king ordered his people to eat only meat and drink only wine, a diet he believed would keep them in sound physical condition. However, several young men of royal blood, who preferred to eat vegetables, objected. So the king allowed these rebels to follow a diet of legumes and water — but only for ten days. When the experiment ended, the vegetarians appeared better nourished than the meat-eaters, so the king permitted the legume lovers to continue their diet.

The first person to establish the principles of human research was the Persian physician Avicenna. In the Canon of Medicine, written in 1020 A.D., he established seven principles for the experimental research of drugs. For example, one rule says that an experiment must be conducted in humans because testing drugs in animals adds nothing to evaluating their effects in humans. All seven principles are used so far in the evaluation of the investigated trials.

Hundreds of years later, in 1747, the famous experiment took place in England. James Lind, a British naval physician, divided the 12 seamen suffering from scurvy into six groups. Each of these groups was given a different specific drug. Only those sailors who regularly

received citrus fruits recovered. Unfortunately, this medical discovery was not fully profited for the next hundred years. It was a significant loss because more people died from scurvy during this time than from the actions of the 100-year Anglo-Spanish War. To commemorate this event, the International Day of Clinical Trials was established in 2005. It falls on May 20, when James Lind started his research [2].

Over the following years, researchers introduced new standards into clinical trial practice. Thus, in 1898 Johannes Fibiger conducted the first randomized trial, i.e., with random allocation of patients, in patients with pertussis, comparing vaccines and the standard treatment of sun exposure. Then, in 1911-1913, Adolf Bingel conducted the first attempt in blinding to evaluate the results of the diphtheria trial. However, the evaluating doctors did not know which drug was given to the patients [3,4].

The creation of the Nuremberg Code was a great achievement of modern times. It was created based on court trials of Nazi doctors who carried out murderous experiments on defenseless prisoners of concentration camps. The Code was published in 1947 and contains a set of 10 principles of ethical research in humans. For the first time, it was written that the patient's free consent is a precondition for participating in research and that the research must have a meaningful and scientific basis.

The principles of Good Clinical Practice (GCP), which are in force worldwide, were published in 1996—the International Conference on Harmonization (ICH) guideline on conducting clinical trials. The document is coded E6 and is also a bioethical standard. The principles of the GCP are primarily based on the findings of the Nuremberg Code findings [5,6,7].

Every clinical trial currently conducted in the world must be consistent with the GCP standards. Thus, the GCP Principles are the most important standard for conducting clinical trials, applying to the researcher, sponsor, and all other persons working on clinical trials. Moreover, their implementation significantly contributed to the qualitative development of experimental medicine [8].

Stages of developing a new drug

The procedure of the new drug introduction to the pharmaceutical market may take even a dozen years. Drug development is a long and expensive endeavor: it takes about 12 years to move from preclinical testing to final approval. It is estimated that it costs approximately $3 billion to develop a new drug, considering the high failure rate, wherein only 10–20% of drugs

tested are successful and reach the market [9]. Creating a new drug and introducing it to the medical market consists of three successive stages. At each stage, the substance's specification is checked, which means that at each stage, the substance may be withdrawn and the process discontinued. In such cases, invested money is lost [10].

The first stage: Preclinical studies

The first stage is preclinical research aimed at developing a new component of the drug ingredient. Patients' needs, knowledge about the disease, and the latest scientific reports are the fundamentals on which the development of a new drug is based. Based on this knowledge, a molecule or many molecules with a similar structure are created and one with the most promising properties is selected. The first tests are then conducted under laboratory conditions. First, whether the selected molecule (which is not yet a drug) produces the desired biological effect is checked. If it can be proved that the new molecule has the expected biological effect, the animal testing phase begins. Next, it checks the potential toxic effects on living organisms. This first stage may take up to several years. When the molecule's efficacy has been confirmed in the predetermined indication, the investor can begin to bring the molecule into clinical trials [11].

The second stage: Clinical trials

According to the WHO definition, a clinical trial is "a study that analyses new diagnostic and therapeutic methods and evaluates their effects on human health" [12]. This is the process that each drug must go through in order for it to be approved for later sale. Its purpose is to check the effectiveness and safety of the molecule.

In order to start clinical trials, the investor must apply for the issuance of a permit to conduct the trial. In Poland, applications are submitted to the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (ORMPMDBP), and the relevant Bioethics Committee. The process of obtaining the opinion of the relevant Bioethics Committee and the permit from the President of the ORMP can be conducted in parallel [13].

The President assesses and reviews such a request within no more than 60 days, counted from the date of submission of full clinical trial documentation. During the procedure for issuing a clinical trial authorization, the President of the Office may request the sponsor to provide supplementary information necessary for the authorization. Inclusion of a patient in the trial

before these requirements are fulfilled is not possible. According to the legislation, the sponsor may start a clinical trial only after obtaining the consent of both authorities [14].

After obtaining consent, the clinical trial of a new molecule goes through 4 successive phases: clinical trials are carried out in the following stages:

- Phase 0. is based on preliminary studies aimed at obtaining information on the pharmacology and distribution of the potential drug and its ability to cross physiological barriers in the body. It is usually based on administering low therapeutic doses of the drug isotope-labeled to a population of 10-15 healthy volunteers.
- Phase I. is run on a small group (20-80) of healthy volunteers. Its purpose is to investigate therapy's safety, potential toxicity, pharmacokinetics, and pharmaco-dynamics (estimation of the minimum and maximum dose, half-life, etc.). Some medicines (such as anticancer or antiretroviral medicines) are being studied in patients with advanced disease.
- Phase II. is run on a larger group (20-300). It aims to test the clinical effectiveness of therapy in a specific disease. This is a study phase that can last up to several years and provides the necessary information for an analysis. The benefit-risk ratio of the investigational drug decides whether to launch another phase III study.
- Phase III. is a randomized study on a large group (300-3000 or more) of patients. It aims to assess the effectiveness of a new therapy fully. Furthermore, it enables assessing the effectiveness, safety, and possible interactions between the tested preparation and other drugs. Researchers confirm the action of a drug in a given indication in a large population of patients and verify whether a given drug is more effective than the previously used standard.
- Phase IV. is also known as the post-registration study, is carried out after the drug is introduced. It aims to confirm the effectiveness and safety of the drug through its long-term use. This stage determines whether the drug is safe in all indications recommended by the manufacturer and for all patients. It also verifies the results obtained in previous phases [15].

Studies on new medicines are conducted on the commission of pharmaceutical companies, while non-commercial studies are conducted mainly by universities, research institutes, associations, and foundations. It is necessary to obtain the appropriate permits, i.e., the consent of the President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products and a favorable opinion of the Bioethics Committee.

Participation in a clinical trial is voluntary and requires appropriate preparation. The investigator who qualifies patients for the study must carefully explain all aspects of the study that are unclear or doubtful to the subject. Informed consent of the patient is necessary for his participation in the clinical trial [16].

Third stage: The registration process

After all phases of non-clinical and clinical research have been positively evaluated, investors move on to the third phase, i.e., introducing the active substance to the market. In the European Union, the European Medicines Agency (E.M.A.) is responsible for this process and regulates four procedures for the registration of medicines:

- National authorization procedures
- Mutual Recognition Procedure (M.R.P.)
- Decentralized Procedure (D.C.P.) based on national law transposing Directive 2001/83/E.C.
- Centralized Procedure (C.P.) based on Regulation (E.C.) No 726/2004 and Directive 2001/83/E.C.

Particular procedures differ in duration, amount of the registration fee, and the area in which the medicine will be authorized. The most important procedure for registering medicines is the C.P., as it involves registering medicine immediately in all E.U. countries. The CP takes place at the E.M.A. and the European Commission issues the marketing authorization decision based on the E.M.A. report. The European Commission uses the scientific opinion of the Committee for Medicinal Products for Human Use (CHMP) in the final decision [17,18,19,20].

The investor shall prepare for E.M.A. the appropriate registration documentation (dossier) for a medical product, consisting of two types of documents. It includes both scientific documents confirming the medicine's quality, safety, and efficacy and administrative documents (registration application and others). The format of the scientific substantiation has been standardized as a Common Technical Document (CTD). The CTD consists of five modules:

- Module 1 provides information on administrative, regional, or national matters of all E.U. countries and a description of the adverse reaction monitoring system. In addition, this module covers detailed administrative data requirements, particularly the application form, the proposed Summary of Product Characteristics (SmPC), package labelling, leaflet. In Poland, the assessment of Module 1 is performed by the

ORMPMDBP, which also decides to include the drug in the Register of Medicinal Products approved for marketing on the territory of the Republic of Poland.

- Module 2 - Contains overviews and summaries of the scientific documentation contained in the following modules: general quality summary, review and summary of non-clinical data and review and summary of clinical data.
- Module 3 - introduces the quality documentation for the medicinal product and information on development studies, substance manufacturing, medicinal product control and stability studies
- Module 4 - contains the results of non-clinical studies and related literature;
- Module 5 contains the results of clinical trials, related literature, data from the available Periodic Safety Update Reports (PSURs), and bioequivalence studies in the case of generic drugs [21].

The medicine's marketing authorization is dependent on a positive assessment by the E.M.A. based on the registration dossier. The dossier must indicate that the medicine is: safe, effective, of adequate quality. The medicine's benefits outweigh the risks associated with its use (positive benefit-risk balance) [22,23]. All anticancer drugs have been registered in E.U. countries and authorized in Poland through a C.P. The registration of new drugs in the E.U., especially immunotherapeutics and drugs already used in new indications, is progressing rapidly and many new registrations should be expected. However, conducting the aforementioned clinical trials and the subsequent drug registration process are extremely costly for investors. For example, the first tyrosine kinase inhibitor (T.K.I.), imatinib, was introduced in 2001 at roughly $30 000 per year of treatment. Now, twenty years later, its price has dropped. However, others, introduced more recently, cost roughly $100 000 per year or more. T.K.I.s exceeded survival benefit expectations; however, they also have a notably high cost [24,25]. The availability of advanced treatment is currently limited for the patient due to the high cost of drugs, dictated by the high cost of research. For now, advanced therapies are available to patients either through government reimbursement or through patient participation in clinical trials. The perspective of being treated with drugs available to patients in clinical trials offers them new prospects for better recovery outcomes. Clinical trials become an opportunity for patients with advanced neoplasm to recover or prolong their lives. However, most clinical trials in Poland and worldwide are conducted in centers located in larger districts or provincial cities. Therefore, patients with the same diagnosis do not always have the opportunity of equal treatment. The described inequality in access to treatment is currently a challenge for health

systems and medical personnel. During the daily medical practice, attention should be paid to the appropriate orientation of doctors to the current therapeutic possibilities in their region. The second option for patients' access to the new therapy is its national reimbursement. The Reimbursement Act has regulated the inclusion of innovative therapies in reimbursement in Poland since 2012. At first, the pharmaceutical company requests reimbursement to the Ministry of Health. Then, the Minister of Health asks for the Agency for Health Technology Assessment and Tariff System (AHTATS) assessment. The AHTATS, commissioned by the Minister of Health, with the participation of external experts, assesses the application. The President of AHTATS issues the final recommendation. Then, the pharmaceutical company and the Minister of Health conduct price negotiations. The Ministry of Health issues the final reimbursement decision. Finally, the drug is entered into the list of reimbursed drugs, foodstuffs for particular nutritional uses, and medical devices under the N.H.F. drug programs. The most common reason for negative AHTATS assessments is the lack of economic justification for the use of innovative therapy. In many cases, treatment is too costly for the state budget. In the case of oncological treatment, it can be assumed that more than 50 000 cancer patients in Poland could benefit annually from various methods of molecularly targeted therapy and immunotherapy. However, standard chemotherapy is currently a relatively cheap treatment. Any new therapy used instead of chemotherapy will cost more and challenge the state budget.

Hematological neoplasms where a new therapeutic approach is the key point of research

Haematological neoplasms are a specific group of diseases in which complete remissions are rarely achieved. Therefore, finding an effective treatment that completely removes these diseases is crucial. Due to this fact, large-scale clinical trials are conducted worldwide, locating, as previously mentioned, mostly in large clinical centers. Therefore, the number of clinical trials in the world and Poland was compared. The clinical trial data was obtained from ClinicalTrials.gov (data cited 7.28.2021). Only those studies with the status "recruiting", "not yet recruiting", or "active not recruiting" were selected for the citation.

Diffuse large B-cell lymphoma (DLBCL)

The most common lymphoma, regardless of age group, is diffuse large B-cell lymphoma (DLBCL). DLBCL is the most common histologic subtype of non-Hodgkin lymphoma

(N.H.L.), accounting for approximately 25 percent of N.H.L. cases. The diagnostic category of DLBCL is heterogeneous in terms of morphology, genetics, and biologic behaviour. Several clinicopathologic entities are now recognized in the 2017 World Health Organization (WHO) classification that is sufficiently distinct to be considered separate diagnostic categories. Diffuse lymphomas are aggressive tumours; therefore, early treatment is essential, without which the patient has a chance of survival for several months. Most relapses occur within the first three years of treatment, and 10% occur more than five years after completion of treatment [26, 27]. Out of 454 trials, 21 DLBCL clinical trials have been launched in Poland [28].

Mantle cell lymphoma (MCL)

Mantle cell lymphoma is a rare tumour of the lymphatic system, but is likely to be aggressive and recurrent. MCL is one of the mature B cell non-Hodgkin lymphomas (N.H.L.). Mantle cell lymphoma (MCL) represents 5–7% of malignant lymphomas, with an annual incidence that has increased over the recent decades to 1–2 cases per 100,000 persons in Western Europe. MCL remains an incurable lymphoma, no plateau in survival curves is observed, and virtually all patients will experience disease recurrence [29]. While most patients with MCL who do not begin therapy will die of their disease within a few years, a small proportion, increasingly better defined, may remain stable for years. These occasional patients with low stage, low-risk disease may have an indolent course, managed by observation, splenectomy, or treatment with alkylating agents analogous to the treatment of patients with small lymphocytic lymphoma or follicular lymphoma. However, MCL is usually diagnosed at an advanced stage and requires systemic treatment. Recurrent disease is treated palliatively and does not lead to a cure. At the moment, no effective treatment is known. Therefore patients are often included in controlled clinical trials [30]. In this case, out of 276 trials, 20 MCL clinical trials have been launched in Poland [31].

Acute myeloid leukaemia (A.M.L.)

Acute myeloid leukaemia (A.M.L.) represents a diverse group of disease entities with the common characteristic of the abnormal clonal proliferation of hematopoietic myeloid precursor cells. The most common acute leukaemia in adults, A.M.L. will be diagnosed in an estimated 0.006% of adults. Approximately 0.003% of adults will die from A.M.L., approximately as many deaths are predicted for all other types of leukaemia combined. It is a disease in which clonal proliferation and accumulation of morphologically and functionally

immature blast cells, derived from neoplastically transformed hematopoietic cells, occurs [32]. The most effective form of therapy remains intensive chemotherapy with or without allogeneic hematopoietic stem cell transplantation (HSCT), a treatment approach with classically high treatment-related morbidity for an elderly population [32,33]. Today's research focuses on the idea of targeted therapy, which would focus on cellular transmission, apoptosis, and the interaction of leukemic cells with the bone marrow lining [34]. Out of 925 trials, 23 A.M.L. clinical trials have been launched in Poland [35].

Chronic lymphoid leukaemia (CLL)

Chronic lymphocytic leukaemia (CLL) is a B cell chronic lymphoproliferative disorder and is characterized by a progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin. CLL is an extremely heterogeneous disease, and most patients have early-stage disease at the time of diagnosis. Therapy is indicated for patients with "active disease" as manifested by advanced stage, high tumour burden, anaemia, thrombocytopenia, or severe disease-related "B" symptoms. There is no single agreed-upon standard front-line treatment regimen for patients with symptomatic or advanced CLL. There are several initial treatment options, and most have not been directly compared. While overall survival rates with the different available regimens are similar, they differ in their complete remission rates, time to progression, and associated toxicities. A choice between these therapies is made based upon patient and disease characteristics and the goals of care [36, 37]. Despite the availability of several treatment options, the heterogeneity of CLL still limits the ability to eradicate the residual disease and prevent relapse [38]. Out of 484 trials, 33 CLL clinical trials have been launched in Poland [39].

Multiple myeloma (MM)

Multiple myeloma (MM) is a plasma cell malignancy representing nearly 10% of all hematological malignancies. Even though the treatment of newly diagnosed multiple myeloma (NDMM), transplant-eligible (T.E.), and not transplant-eligible (N.T.E.) patients has remarkably improved over the years and multiple treatments are available, the disease will eventually relapse as MM remains not curable. Therefore, treating MM is a challenge, and finding the appropriate strategy to increase survival is the key issue. Patients may experience symptoms such as bone pain, features of chronic kidney disease, including acute renal failure. Also, hypercalcemia and anaemia are observed in most patients. Palliative care is provided for

patients undergoing active treatment and those whose further treatment has been abandoned [40]. Out of 953 trials, 39 MM clinical trials have been launched in Poland [41].

Myelodysplastic syndromes (M.D.S.)

Myelodysplastic syndromes are the most common group of bone marrow malignancies, mainly diagnosed in the elderly. Myelodysplastic syndromes (M.D.S.) are clonal hematopoietic stem cell disorders characterized by ineffective erythropoiesis, dysplasia involving one or more cell lineages, peripheral cytopenia. The diagnosis of M.D.S. should always be considered in any case of prolonged cytopenia. In young patients, bone marrow transplantation should be considered, while in older patients, qualification for symptomatic treatment is made. The median O.S. for M.D.S. patients ranges from 6 to 54 months [42,43]. Out of 649 trials, 18 M.D.S. clinical trials have been launched in Poland [44].

Clinical trials in haematology in Poland

In order to determine at which sites and in which location in Poland clinical trials in haematology are conducted, a summary data set was downloaded from the ClinicalTrials.gov summary analysis (aact.ctti-clinicaltrials.org), which combines data from ClinicalTrials.gov into an editable database. A script was created in the R package to extract the studies of interest. Initially, the list of clinical trials was narrowed down to those with sites in Poland. Then, the list was reduced to clinical trials in haematology; the list of diseases from the "Blood and Lymph Conditions" category from the ClinicalTrials.gov website was used to extract those trials. In the end, 276 clinical trials were obtained.

The distribution of locations of conducted trials on the map of Poland is highly diverse. Clinical trials are registered in every province in Poland. The smallest number of clinical trials is recorded in Lubuskie Province and the largest in Mazowieckie Province. There is a precise concentration of research centers in provincial cities, to which medical universities and clinical hospitals are subordinate. The largest number of studies is located in Warsaw. The five cities in Poland with the highest number of registered research, apart from Warsaw, are Kraków, Gdańsk, Wrocław, and Łódź.

The main centers conducting clinical trials in Poland are academic units, teaching hospitals, and university hospitals. At the top of this list is the Institute of Haematology and Transfusiology in Warsaw. In addition to university institutions, locations conducting clinical trials, but with a much smaller number of assigned trials, also include private centers

specializing in directing clinical trials, private medical practices, and outpatient clinics. It shows the uneven distribution of centers specialized in clinical trials in Poland. This creates unequal access to treatment methods for patients and thus creates a privileged position for patients living in larger cities.

Future perspective, a challenge for current medicine

Clinical trials investigating new therapy concepts are of high interest to patients with severe and life-threatening conditions such as cancer. As mentioned in the section on haematological diseases, most haematological malignancies have a poor prognosis for the patient and are associated with a higher risk of death. Therefore, it is important to introduce clinical trials in new hospital treatment centers to provide patients with greater possibilities and potentially more effective than existing therapeutic methods. Unfortunately, there are only 276 open clinical trials in Poland in the field of haematology. Some of these trials are conducted in more than one center. Therefore, the absolute value of different clinical trials is less than 276. Nowadays, in Poland, it is conducted 103 different clinical trials in 21 different centers. They mainly take place in large cities: academic units, teaching hospitals, and university hospitals. This situation does not provide a balanced supply for all patients, regardless of where they live.

The distribution of clinical trials is also uneven across Europe. On average, Eastern Europe has seen one-third fewer such trials than Western Europe, for example. For the same period, phase III clinical trials (all indications) were distributed relatively equally. Numerous regulatory and legal barriers make the conduct of pan-European clinical trials challenging for sponsors. Based on the E.U.'s principle on freedom of movement, participation in a clinical trial abroad is theoretically possible. While there is no specific European legislation on the facilitation of cross-border clinical trial participation, frameworks exist [45,46].

Another challenge to medicine in clinical trials is the disproportion between the age groups that are qualified for testing the molecule and in the subsequent stages of its approval for use. Available evidence indicates that enrolment rates in hematologic malignancy trials remain low for older patients, particularly for those adults 75 years and older. As the median age at diagnosis for most haematological malignancies is 65 years or older, and a significant proportion of patients diagnosed are 75 years and older, new and current cancer therapies that are approved are likely to be used in these patient groups. Biological and clinical differences between older and younger adults and diversity within older patients necessitate adequate

representation of the older subpopulation in hematologic malignancy trials. Older patients have more comorbidities than the general population, which implicates different pharmacokinetics and drug metabolism. It may result in a potentially higher risk of side effects in the older age group. Representation of these patients in hematologic malignancy trials may increase our knowledge about the treatment effects of cancer therapies in the older adult population. However, several barriers to enrolment exist and extensive collaboration is required to incorporate and evaluate the success of current strategies such as broadening eligibility criteria to enhance enrolment of older adults with hematologic malignancies in clinical trials. These approaches are needed to resolve residual uncertainties in the care of older adults with hematologic malignancies. Greater popularity and availability of clinical trials will undoubtedly contribute to more reliable test results and more precise indications [47].

One more challenge for modern medicine is the reasonable availability of interventions proven to be useful during research trials. Medicines that are registered under the central procedure are authorized in the E.U., but this does not mean that they are reimbursed by the national health care systems of the E.U. Member States. As a result, the cost of selling the new drug is extremely high due to the funds invested in its production and subsequent clinical trials. Without reimbursement, the amount associated with purchasing a new drug often exceeds the financial capacity of Polish citizens [25,48].

Clinical trials are an integral part of the development of modern medicine, without which effective and personalized therapies cannot be developed. Thanks to the development of science, many recommendations and restrictions have been created to protect the patient and ensure that his health does not deteriorate due to the clinical trial. As a consequence of the above, it should be considered that drug development to its national distribution is very complicated and takes a long time. Therefore, despite the proven effective action of the drug, patients often do not have access to it. This problem is addressed to national governments, sponsors, pharmaceutical companies, and doctors, which could increase the availability of effective drugs for patients in the future by informing patients about new therapies, conducting an appropriate health policy, simplifying legislation and reimbursement.

References

1. Emanuel E.J., Wendler D., Killen J., Grady C.: What makes clinical research in developing countries ethical? The benchmarks of ethical research. Journal of Infectious Diseases, 2004, 189(5), 930–937.

2. Cochrane, Clinical Trials Day https://www.cochrane.org/news/clinical-trials-day-2021 (cited: 13.07.2021).
3. Collier R.: Legumes, lemons and streptomycin: A short history of the clinical trial. Canadian Medical Association Journal, 2009, 180(1), 23-24.
4. Bhatt A.: Evolution of clinical research: a history before and beyond james lind. Perspectives in Clinical Research, 2015, 1(1), 6-10.
5. Ghooi R.B.: The Nuremberg code--a critique. Perspectives in Clinical Research, 2011. 2(2), 72.
6. Otte A., Maier-Lenz H., Dierckx R.A.: Good clinical practice: historical background and key aspects. Nuclear Medicine Communications, 2005, 26(7), 563–574.
7. Leaning J.: War crimes and medical science. British Medical Journal Publishing Group, 1996, 313(7070), 1413–1415.
8. Vijayananthan A., Nawawi O.: The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomedical Imaging and Intervention Journal, 2008, 4(1), e5.
9. Rajkumar S.V.: The high cost of prescription drugs: causes and solutions. Nature Publishing Group, 2020, 10, 71.
10. Horien C., Yuan P.: Focus: drug development: drug development. Yale Journal of Biology and Medicine, 2017, 90(1), 1.
11. Chen J., Luo X., Qiu H., Mackey V., Sun L., Ouyang X.: Drug discovery and drug marketing with the critical roles of modern administration. American Journal of Translational Research, 2018, 10(12), 4302.
12. WHO, clinical trials https://www.who.int/health-topics/clinical-trials/ (cited: 13.07. 2021).
13. Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Registration under national procedure http://www.urpl.gov.pl/en/biocidal-products/biocidal-products-registration/registration-under-national-procedure (cited: 13.07. 2021).
14. Waligora M.: Failures in clinical trials in the European Union: Lessons from the Polish experience. Science and Engineering Ethics, 2013, 19(3), 1087–1098.
15. Ministry of Health, Marketing authorization https://www.gov.pl/web/zdrowie/pozwolenie-na-dopuszczenie-do-obrotu1 (cited: 13.07.2021).
16. Clinical trials in Poland https://pacjentwbadaniach.abm.gov.pl/pwb/badania-kliniczne (cited: 13.07.2021).

17. Kohler M.: Regulatory pathways in the European Union. MAbs, 2011, 3(3), 241–242.
18. Detela G. Lodge A.: E.U. regulatory pathways for ATMPs: standard, accelerated and adaptive pathways to marketing authorisation. Molecular Therapy - Methods and Clinical Development, 2019, 13, 205–232.
19. Regulation (E.C.) No 726/2004 of the European Parliament and of the Council of March 31 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726 (cited: 13.07.2021).
20. Directive 2001/83/E.C. of the European Parliament and of the Council of November 6 2001 on the Community code relating to medicinal products for human use https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32001L0083 (cited: 13.07. 2021).
21. Maliepaard M., Taams A.C., Sung C., Poh J., Yu Y.: Ethnicity-Specific Drug Safety Data in European Medicines Agency Registration Dossiers, European Public Assessment Reports, and European and Singapore Drug Labels: Lost in Translation? Pharmaceutical Medicine, 2019, 33(5), 407–416.
22. Mohammed Y.M.: Regulatory pathways for development and submission activities. MedWrit, 2019, 28, 8–19.
23. Vogel A.M.: Hybrid or mixed marketing authorization application in the european union: not a trivial decision in new development programs for established drugs. Drug Information Journal: Information for Authors, 2012, 46(4), 479–484.
24. Saret C.J., Winn A.N., Shah G., Parsons S.K., Lin P.J., Cohen J.T., Neumann P.J.: Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses. Blood, 2015, 125(12), 1866-1869.
25. Abboud C., Berman E., Cohen A., Cortes J., DeAngelo D., Deininger M., Devine S., Druker B., Fathi A., Jabbour E., Jagasia M., Kantarjian H., Khoury J., Laneuville P., Larson R., Lipton J., Moore J. O., Mughal T., O'Brien S.: The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood, 2013, 121(22) 4439–4442.
26. Arber D.A.: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia. Blood, 2016, 127(20), 2391–2405.

27. Warzocha K., Puła B.: Rozpoznawanie i leczenie chorych na chłoniaka rozlanego z dużych komórek B. Hematologia, 2017, 8(2), 113–131.
28. DLBCL clinical trials registered in Poland in 2021 https://clinicaltrials.gov/ct2/results?cond=DLBCL&term=&cntry=PL&state=&city=&dist= (cited: 13.07.2021
29. Visco C., Di Rocco A., Evangelista A., Quaglia F.M., Tisi M. C., Morello L., Zilioli V. R., Rusconi C., Hohaus S., Sciarra R., Re A., Tecchio C., Chiappella A., Marin-Niebla A., McCulloch R., Gini G., Perrone T., Nassi L., Pennese E., Stefani P.M., Cox M.C., Bozzoli V., Fabbri A., Polli V., Ferrero S., Celis M.I.A., Sica A., Petrucci L., Arcaini L., Rule S., Krampera M., Vitolo U., Balzarotti M.: Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: Results from the MANTLE-FIRST study. Leukemia, 2021, 35(3), 787–795.
30. Hanel W., Epperla N.: Emerging therapies in mantle cell lymphoma. Journal of Hematology & Oncology, 2020, 13(1), 1–18.
31. MCL clinical trials registered in Poland in July 2021 https://clinicaltrials.gov/ct2/results?cond=MCL&term=&cntry=PL&state=&city=&dist= (cited: 13.07. 2021).
32. Saxena K., Konopleva M.: An expert overview of emerging therapies for acute myeloid leukemia: Novel small molecules targeting apoptosis, p53, transcriptional regulation and metabolism. Expert Opinion on Investigational Drugs, 2020, 29(9), 973–988.
33. Juliusson G., Lehmann S., Lazarevic V.: Epidemiology and Etiology of A.M.L. Acute Myeloid Leukemia Springer, 2021, 1–22.
34. Gui P., Bivona T.G.: Stepwise evolution of therapy resistance in A.M.L. Cancer Cell, 2021, 39(7), 904-906.
35. A.M.L. clinical trials registered in Poland in July 2021 https://clinicaltrials.gov/ct2/results?cond=Aml&term=&cntry=PL&state=&city=&dist= (cited: 13.07.2021).
36. Mukkamalla S.K.R., Taneja A., Malipeddi D.:. Chronic Lymphocytic Leukemia. StatPearls Publishing, 2021.
37. Bewarder M., Stilgenbauer S., Thurner L., Kaddu-Mulindwa D.: Current Treatment Options in CLL. Cancers (Basel), 2021, 13(10), 2468.
38. Ostasov P., Robertson H., Piazza P., Datta A., Apperley J., Houdova L., Lysak D., Holubova M., Tesarova K., Caputo V.S., Barozzi I.: Evolution of advanced chronic lymphoid leukemia unveiled by single-cell transcriptomics: a case report. Frontiers in Oncology, 2020, 10, 2356.

39. CLL clinical trials registered in Poland in July 2021 https://clinicaltrials.gov/ct2/results?cond= CLL&term=&cntry=PL&state=&city=&dist= (cited: 13.07.2021).
40. Bobin A., Liuu E., Moya N., Gruchet C., Sabirou F., Lévy A., Gardeney H., Nsiala L., Cailly L., Guidez S., Tomowiak C., Systchenko T., Javaugue V., Durand G., Leleu X., Puyade M.: Multiple myeloma: An overview of the current and novel therapeutic approaches in 2020. Cancers, 2020, 12(10), 2885.
41. MM clinical trials registered in Poland in July 2021 https://clinicaltrials.gov/ct2/results?cond=Multiple+Myeloma&term=&cntry=PL&state=&city=&dist= (cited: 13.07.2021).
42. Dass J., Kotwal J.: Myelodysplastic Syndrome: An Overview. Hematopathology, 2019, 149–161.
43. Zahid M.F., Malik U.A., Sohail M., Hassan I.N., Ali S., Shaukat M.H.S.: Cytogenetic abnormalities in myelodysplastic syndromes: an overview. International Journal of Hematology-Oncology and Stem Cell Research, 2017, 11(3), 231.
44. M.D.S. clinical trials registered in Poland in July 2021 https://clinicaltrials.gov/ct2/results?cond=MDS&term=&cntry=PL&state=&city=&dist= (cited: 13.07.2021).
45. Lalova T., Padeanu C., Negrouk A., Lacombe D., Geissler J., Klingmann I., Huys I.: Cross-Border Access to Clinical Trials in the E.U.: Exploratory study on needs and reality. Frontiers in medicine, 2020, 7.
46. All clinical trials in Europe in July 2021 https://clinicaltrials.gov/ct2/results/map/click?map.x=739&map.y=251&mapw=1515 (cited: 13.07.2021).
47. Kanapuru B., Singh H., Kwitkowski V., Blumenthal G., Farrell A.T., Pazdur R.: Older adults in hematologic malignancy trials: representation, barriers to participation and strategies for addressing underrepresentation. Blood Reviews, 2020, 43, 100670
48. Moore T. J., Heyward J., Anderson G., Alexander G. C.: Variation in the estimated costs of pivotal clinical benefit trials supporting the U.S. approval of new therapeutic agents, 2015--2017: a cross-sectional study. B.M.J. Open, 2020, 10(6), e038863.

Distance learning in medical education: forms and methods, examples of application in selected countries, own experience

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Introduction

In the era of the worldwide COVID-19 pandemic, education in Poland was faced with the need to organize distance learning at all educational stages, including higher education. Unfortunately, both the teaching staff and pupils, students, and listeners were not prepared for this new educational situation.

Terminology

Distance learning is one of the forms of education. It is also referred to as "distance education", "distance teaching", "distributed learning"," distributed education", "remote learning", "remote education", "remote teaching", "online learning", "e-learning", "e-education", "e-teaching", "virtual education", "telematic education" [1–3]. However, these terms have different meanings. The broadest of them is distance education, defined by Mirosław Kubiak as "a method of conducting the didactic process in conditions where teachers and pupils (students) are distant from each other (sometimes significantly) and are not located in the same place, using - in addition to traditional methods of communication - also modern, very modern telecommunications technologies, e.g., sending voice, video, computer data and printed materials. Modern technologies also enable direct real-time contact between the teacher and the student via audio- or videoconferencing, regardless of the distance between them" [2,4]. A narrower concept is e-learning, considered as part of distance education, which uses all available electronic media, such as the Internet, intranet, extranet, satellite links, audio and video documents, interactive television [2,5]. It should be noted that distance learning is, in fact, one of the methods of education, another form of organization of didactic processes, which

enables teaching content to be directed to dispersed groups of students and does not require direct, personal meetings between the teacher and students. Therefore, a teaching method introduces indirect contact instead of direct contact between the learner (student) and the teacher (professor). On the other hand, e-education is a set of tools enabling this process's implementation and carrying out. They are to support the university, whose task is to shape attitudes and competencies and support and strengthen the process of lifelong learning [6–8].

While the concept of distance learning may seem like a new term, it was first used almost 100 years ago. In the beginning, it was of a correspondence nature, consisting in sending back tasks that had been solved by students and sent earlier by the educational institution. In the following years, such teaching was enriched with courses on audio and video cassettes. There was also an educational radio and television. However, the real breakthrough in distance education took place in the nineties with the discovery and spread of the Internet, which allowed for the development of new possibilities of communication and interaction of the learning group and close to traditional teaching, real contact of students with the teacher [9].

Distance learning applies to many aspects of learning. It can be one of the basic methods of teaching, training and self-education, especially for adults. For teachers, including academic teachers, it is a chance to raise and improve their professional qualifications throughout their lives through the implementation of courses, trainings or classes as part of postgraduate studies [10].

Advantages and disadvantages of distance learning

The advantages of distance learning include saving time and reducing training costs by eliminating travel and accommodation expenses. In addition, by removing the time and space barriers, this form of education allows many people to study, e.g., the disabled and all those for whom access to the university for some reasons is difficult or impossible (e.g., women dealing with raising children). It also enables individual management of the course of study and flexibility in the education process (choosing the time, forms, and methods). Additionally, it develops self-discipline and independence and shapes the organizational sense of students [1,5,8–11].

Distance learning, unfortunately, is not free from disadvantages, including the lack of direct teacher-student contact (depersonalization of education), the inability to learn all content

and participate in functional activities, e.g., laboratory, experimental, design, etc., the need for diversified and expensive equipment, especially a computer connected to the Internet, the need to use a computer, network and advanced programs dedicated to distance learning, and the lack of a stimulating atmosphere for learning typical for a school or group [1,8,9,11].

Forms and methods of distance learning

The available literature distinguishes many forms and methods of distance learning, and the division is made according to various criteria. Most often, four basic forms of teaching are distinguished, and one of the division criteria is the time availability/mode of participation:

Synchronous learning

Synchronous learning takes place in real-time, allowing for real direct communication between the teacher and students via electronic means of communication, e.g., chat, instant messaging applications, tele- / videoconference, virtual whiteboard [5,12–15]. Examples of instant messaging applications used in synchronous learning include the ZOOM or Microsoft Teams applications.

Asynchronous learning

Asynchronous learning is not real-time. Instead, it consists in acquiring didactic material by the learner without ongoing contact with the teacher. The means of communication used include [5,8,12–15]:

- e-mail,
- discussion forum,
- interactive multimedia courses,
- simulations,
- libraries of e-books and lectures recorded on video,
- program tutorials,
- broadly understood Internet sources (including the so-called search engines)

Self-education

Self-education, also referred to as individual education, is characterized by a complete lack of contact between the participants of the didactic process. Tools similar to those in the

asynchronous model are used here. However, the main difference is that the student himself decides about the pace of learning and the subject of the courses [5].

Blended learning

Blended learning, otherwise known as hybrid or complementary, combines distance learning and traditional learning [11,13–16]. In practice, it is the most common form of teaching that seems to be the future of education, particularly in medical science.

The division into four generations of methods used in distance learning is also commonly described, and the division criterion is the type of technique used. This division also takes into account the historical approach.

First-generation distance learning system - correspondence model

In the first generation of education, teaching materials are mainly in paper form. In addition to correspondence, scripts, and textbooks, printed materials and lessons broadcast by radio are used. The correspondence model allows students to choose the time, place and pace of learning freely. It lacks methods of student-teacher interaction. It was introduced in the 18th century.

Second generation distance learning system - teleeducational model

Second-generation education uses audio and video communication, radio broadcasting (1920), television broadcasting (1950), and audio and video conferencing.

Third generation distance learning system - multimedia model (1970)

In the third generation of education, printed materials and multimedia resources such as audio and video cassettes/discs are used. This model also uses Computer Assisted Learning (CAL, Computer-based training - CBT) as an interaction tool and interactive video.

Fourth-generation distance learning system - a virtual model

The fourth generation of education is based on the use of the Internet to provide educational content as well as communication between teacher and student and between students. This model is assumed by Computer Mediated Education (CME) and Web-based training (WBT). Modern technologies and Internet services enable the use of high-quality multimedia educational content and advanced interaction mechanisms.

The **fifth** or even **sixth generation distance learning system** is being described more and more often. These terms were created due to the evolution of Internet technologies to the form of Web 2.0 and Web 3.0. They include, among others, computer simulations or virtual reality 3D [6,12,17–20].

Other, less frequently distinguished types of methods and forms of distance learning, depending on the adopted division criterion, are:

Division according to the **student-teacher relationship**:

- Courses with the teacher, e.g., in asynchronous or synchronous modes
- Courses without the teacher, but based on multimedia courses (programmed learning)
- Self-study, based on various types of information available in electronic form

Division according to the **relation to traditional education**:

- complementing traditional education
- replacing traditional education

Division according to the **degree of formalization**:

- "Formal" learning - closely related to the university's curriculum, structured, e.g. related to the ECTS system
- Informal learning is an integral form of academic teaching, but developing and appreciated more and more, complementing traditional classes [12].

Distance learning in medical education

In my opinion, the specificity of medical education and the nature of work in medical professions prevent the introduction of complete distance learning. In this area of education, direct contact between the teacher and the student, as well as the student and the patient, is irreplaceable, as it allows to acquire practical skills and gain experience necessary in medical science and the competences necessary to properly build the doctor-patient relationship, which are the basis of the medical profession. Therefore, the saying of Cicero *Usus est optimus magister* (practice is the best teacher) remains relevant [16].

The solution to this problem is blended learning combining elements of distance and traditional education. In medical education, theoretical classes can be implemented as distance learning in asynchronous or synchronous learning (lectures, seminars). After acquiring the necessary knowledge, the student can effectively acquire practical skills in the traditional form

(practical and clinical exercises). This form of teaching in medical education seems to have several advantages over only traditional education. Medical sciences are one of the most difficult, and their assimilation requires much time from the student. The implementation of theoretical classes in a remote form allows you to save time for commuting, additionally increases the comfort of teaching, because it eliminates long, often several hours breaks between subsequent classes at the university, which requires the student to travel several times in one day or wait for classes in unsuitable places (cafes, cloakrooms). Hospital departments are also often unprepared to provide theoretical teaching in infrastructure, and blended education does not have this problem. In addition, this teaching model allows you to focus entirely on practical aspects during face-to-face activities with the teacher. Tools for remote knowledge checking available on the market (e.g., Moodle platform, Testportal) allow for immediate verification of knowledge and obtaining examination results and statistics, and in the case of subjects in which exams take the "oral" form, they can be effectively carried out using tools for videoconferences (e.g., ZOOM, Microsoft Teams).

Medical education does not only take place at the level of higher education. The continuous progress of medical science and the constant discoveries mean that medics have to educate themselves throughout their lives. E-learning allows scientists from all over the world to exchange experiences without leaving home, which saves time and money. An important advantage of e-learning is the possibility of obtaining knowledge from telemedicine databases located in many places around the world and offering a collection of various information (such as e.g., scientific publications, epidemiological or statistical data, etc.) in every field of medical activity [13].

Additionally, telesurgery is becoming a new and interesting medical direction. This term means performing remote surgeries via internet links using a remote-controlled surgical robot. For example, in 2001, New York surgeons performed a successful gallbladder removal operation on a 68-year-old female patient in an operating room in Strasbourg, France, 6,500 km away. Because of such opportunities, it seems important to introduce this form of treatment into the medical education program [21].

Distance learning in medical education in selected countries

The choice of the countries described in the paper results from the available literature.

Bosnia and Herzegovina

Although Bosnia and Herzegovina is the penultimate country in Europe to use internet technologies, the University of Sarajevo has made significant efforts to improve the low digital literacy of the university and physicians. In October 2003, the University of Sarajevo started distance learning by opening the University Distance Learning Center.

The first of the subjects realized within distance learning was the subject of medical informatics. As part of the educational platform (www.e-learning.ba), 11 asynchronous lectures were made available. Within the platform, in addition to materials, you can download and upload: practical papers, seminars, information, recommended links, plans, and programs, quizzes, schedule, recommended reading exam schedule, and exam results. The exam in the subject is also carried out remotely using the tools available on the platform. Since 2002, at the Medical faculty of the University of Sarajevo at Cathedra for Medical informatics, the project entitled: "Possibilities of introducing distance learning in the medical curriculum" was approved by the Federal and the Cantonal Ministry of science and education, was carried out. The project aimed to improve the education process in biomedical fields using modern methods, methodologies, and information technologies, by the strategy and goals declared in the Bologna Declaration. The Cathedra of medical informatics and the Cathedra of Family medicine at the Medical Faculty of the University of Sarajevo began to use e-education as a standard way of teaching medical students. Synchronous content delivery is difficult to achieve in medical education without certain prerequisites required in the biomedical faculties of Bosnia and Herzegovina: high-speed internet connections, free access to computers, and computer skills of students and teachers [22].

Jordan

In Jordan, before the COVID-19 pandemic, distance learning technologies were not used in medical education. In May 2020, a cross-sectional survey based on a questionnaire was conducted among final-year students (4-6 years) of all medical universities in Jordan aimed at examining the situation of distance learning among medical students during their clinical years and identifying possible challenges, limitations, satisfaction, and also their perspectives in this way of teaching. Most of the remote classes were conducted in a synchronous form in the form of live videoconferences (approx. 80%), previously recorded video materials were used less frequently. Various platforms and applications were used to implement the classes, including ZOOM (most often), Microsoft Teams, WhatsApp groups, Facebook groups, YouTube,

Moodle, and Skype channels. The authors of the paper postulate that distance learning may partially replace the traditional method of delivering theoretical but not clinical skills. They believe that a blended approach (traditional and e-learning) will be most appropriate for future medical training [23].

Pakistan

Most Pakistani medical schools still have not introduced information technology in teaching medicine. Higher education organizations are reluctant to embrace modern trends in medical education, and the concepts of distance learning, blended learning, and online courses are not very popular in Pakistani medical schools. Many medical universities in the country lack specialists in the field of information technology. As of 2017, only two medical schools actively use distance learning through the Moodle platform. Only a few medical institutions offer blended postgraduate courses using distance learning in Pakistan [24].

South Korea

According to a 2006 survey of Korean medical schools, only 6% offered some form of online education. In addition, only 7 of the 41 medical schools in Korea replied that they plan to use distance education in their curriculum. The main barrier would be the huge amount of medical information that needs to be turned into e-learning content, which is an often insurmountable difficulty for one person or institution. The situation has been confused by increasing pressure on medical faculties to increase research and clinical productivity. Additionally, the lack of support from the academic staff, especially in terms of budget and e-learning staff, discouraged them from distance learning. In addition, medical faculty staff had few professional development opportunities to deepen their understanding of distance learning in medical education. Therefore, Korean medical schools faced serious challenges related to the introduction of e-learning.

Accordingly, the Korean Consortium for e-Learning in Medical Education (e-MedEdu) was established in 2007. Currently, 36 out of 40 Korean medical schools participate in the consortium, which has grown from 25 schools since 2007. It was created to work together to deliver high-quality online educational resources for medical schools across the country. This e-learning strategy aims to improve the quality of medical education at the national level by providing students with equal access to high-quality educational resources and supporting

independent learning, thereby increasing the effectiveness and efficiency of developing online educational resources by sharing the necessary resources between medical colleges. The consortium also plans to make e-learning content available to medical schools in other countries, involving more medical schools in the consortium and sharing e-learning content developed by other institutions or consortia. The consortium is also researching and developing effective online learning strategies for medical education, including interactive virtual patient cases and other innovative pedagogical approaches using Web 2.0 technologies.

The consortium has developed a portal where lecturers and students associated with partner schools have access to numerous educational resources (www.mededu.or.kr). The website was opened to medical students in member schools in fall 2008. This e-learning portal provides functions to create and publish various learning objects suitable for medical education, including virtual patient cases, image banks, online quizzes, and videos. The learning facilities developed by the consortium are primarily intended for self-study use by students. In addition, faculty members can use online resources to complement their in-class teaching by referring to the cases they talk about when giving lectures or by referencing materials for training assignments [25].

India

In India, most of the distance learning activities carried out by medical college students are limited to data searches for thesis and research work. The use of technology in medical education in other areas is in its early stages. Two medical colleges (St. John's Hospital, Bangalore, and Christian Medical College, Vellore) use the TUSK platform for distance learning, especially to build support for their students to work in rural and neglected areas in India by strengthening their learning effort. TUSK software includes syllabuses, slides, lecture recordings (audio and video), class schedules, course assessments, section guides, quizzes and case reports, grade books, and other resources provided by the faculty. Online Google groups are used extensively by the Medical Council of India for training in medical subjects as part of an annual medical education scholarship at ten nodal centers in India. A listserv is an e-learning platform within the FAIMER fellowship run at various centers in India. Postgraduate students also benefit from Internet broadcasts provided by professional organizations such as the Indian Academy of Pediatrics. Edusat lectures are conducted daily for medical students in Punjab. Despite these efforts, e-learning has reached very few medical schools [26].

Liberia

In Liberia, medical education takes place at only one university - the College of Health and Life Sciences (COHLS). In 2016-2017, e-learning solutions were implemented at the university. The whole process was carried out in several stages. The initial stage was to identify problems related to the implementation of distance learning. The main ones included: very limited access to computers, no internet connection, power outages and a lack of information technology skills. The next three stages included infrastructure implementation and workshops to train teachers and students to use remote learning tools. Teaching was conducted in the form of synchronous and asynchronous education [27].

Poland - own experience - first author's experience

In Poland, the popularization of distance learning in academic medical education was forced by the epidemiological situation related to the COVID-19 pandemic. During my studies at the Wroclaw Medical University in medicine, I encountered distance learning only once as a student - it was a library training carried out as an optional subject.

During my third-cycle studies at the Doctoral School, I have experience with distance learning, both from the perspective of the student and the teacher. Remote teaching in Poland at medical universities is not systemically structured. The forms and tools for implementing distance learning are determined individually by a specific university and sometimes differ depending on the subject. Distance education at the Wroclaw Medical University is carried out in the form of blended education in clinical subjects or only remote education in the case of theoretical subjects and as part of third-cycle studies. Theoretical classes are carried out in the form of synchronous, asynchronous, or self-education. The tools used to conduct the classes include mainly applications that allow for videoconference - ZOOM, Microsoft Teams, BigBlueButton Platform. The Moodle platform that allows conducting tests and clouds and e-mail, which allow sending materials for asynchronous classes or self-education, are also used.

Remote learning in medical education is offered not only by universities but also by private companies. Internet courses preparing graduates of medical universities for the state examination allowing them to obtain the license to practice the profession of a doctor or dentist are very popular. One of them is the “Więcej niż LEK” course offered by Bethink, which prepares medical graduates for LEK - Medical Final Examination (*Lekarski Egzamin*

Końcowy). From 2019, I have the pleasure to be one of the moderators - content supervisors of this course. The course consists of constantly updated presentations enriched with audio, video, patient cases and open and closed control questions. Participants are under constant moderator's care, thanks to which it is possible to dispel doubts that arise during the assimilation of the material. Students receive a course plan with a timetable for implementing the lessons, which greatly facilitates the preparation for the exam. Additionally, the course includes an introductory course on practical learning and an album of mind maps. In 2020, due to the COVID-19 pandemic and the lack of infrastructure necessary for distance learning at many universities, as well as the overlap between the course material and the curriculum for the 6th year of the medical faculty, several medical universities in Poland started cooperation with Bethink and purchased access to the course for final year students - incl. Lazarski University in Warsaw, Medical University of Warsaw, Zielona Góra, Medical University of Bialystok.

One of the important elements of medical education is self-study. In order to get acquainted with the latest medical achievements, it is worth referring to international literature and foreign websites dedicated to medics, containing current guidelines, scientific publications, medical films, or a database of imaging test results. Examples of tools used by me are the websites:

- https://medtube.pl - online training platform containing videos, courses, images, webinars, documents
- https://radiopaedia.org – international encyclopedia of radiology
- https://scholar.google.com, https://pubmed.ncbi.nlm.nih.gov – scientific publication search engines
- https://www.medscape.com, https://www.uptodate.com/home - databases addressed to clinicians and students containing information on pathological conditions and guidelines for conduct based on the principles of EBM (Evidence Based Medicine)

Summary

In summary, distance learning as part of hybrid education can be an effective tool used in medical education. Because of the constant technological progress, widespread access to computers and the Internet, and the growing number of applications adapted to conducting distance learning, it seems likely that distance education will become a common form of

education at universities, also in medical faculties. It is becoming essential to introduce systemic solutions aimed at structuring distance learning based on legal regulations. It is also necessary to conduct intensive training of academic staff in e-learning to use the available tools most effectively. It is also necessary to create a dedicated department within the university structure responsible for the technical aspect of distance learning so that lecturers can fully focus on the teaching process.

References

1. Dziewulak D.: Kształcenie na odległość w wybranych państwach europejskich. Analizy BAS, 2012, 18(85), 11.
2. Guri-Rosenblit S.: "Distance education" and "e-learning": Not the same thing. Higher Education, 2005, 49, 467–493.
3. Guri-Rosenblit S.: E-teaching in higher education: An essential prerequisite for e-learning. Journal of New Approaches in Educational Research, 2018, 7(2), 93–97.
4. Kubiak MJ.: Szkoła, Internet, Intranet. Wirtualna edukacja. Wydawnictwo MIKOM, Warszawa, 2000.
5. Nahotko M.: Nauczanie Zdalne (E-Learning) W Polskich Szkołach Wyższych / e-TEN EURIDICE [w:] E-włączenie czy e-wyobcowanie? : e-inicjatywy bibliotek, archiwów, muzeów i uczelni w walce z alienacją społeczną w Polsce i na świecie. Kocój M. (red.). Instytut Informacji Naukowej i Bibliotekoznawstwa Uniwersytetu Jagiellońskiego, Kraków, 2006, 62–66.
6. Kopciał P.: Analiza metod e-learningowych stosowanych w kształceniu osób dorosłych. Zeszyty Naukowe WWSI, 2013, 9(7), 79–99.
7. Wagner J.: Kształcenie na odległość w edukacji całożyciowej. Dyskursy Młodych Andragogów, 2015, 16, 163–173.
8. Żołędowska-Król B.: Nauczanie na odległość formą edukacji w szkolnictwie wyższym. Zeszyty Naukowe Wyższej Szkoły Humanitas Zarządzanie i Marketing, 2007, 1, 79–85.
9. Smal T.: Nauczanie na odległość (e-learning). Zeszyty Naukowe/Wyższa Szk Oficerska Wojsk Lądowych im. gen. T. Kościuszki, 2009, 3(3), 105–14.
10. Kuźmińska-Sołśnia B.: Nauczanie zdalne – istota zawartości stron webowych. [w:] Informatyka w dobie XXI wieku: technologie informatyczne w nauce, technice i edukacji. Jastriebow A. (red.). Radom, 2009, 217–220.

11. Jakubczak B.: Kształcenie zdalne przez Internet jako urzeczywistnienie idei edukacji bez granic. [w:] Edukacja bez granic mimo barier. Czajkowska A., Rondalska D. (red.). Wydawnictwo Wyższej Szkoły Bezpieczeństwa, Poznań, 2011, 398–406.
12. Wodecki A.: Po co e-learning na uczelni? [w:] E-learning w kształceniu akademickim. Dąbrowski M., Zając M. (red.). Fundacja Promocji i Akredytacji Kierunków Ekonomicznych, Warszawa, 2006, 9–14.
13. Kononowicz A., Pyrczak W., Roterman-Konieczna I.: E-learning in medicine. Problemy Higieny i Epidemiologii, 2006, 87(4), 364–371.
14. Heba A.: Nauczanie na odległość - wczoraj i dziś. Nauczyciel i szkoła, 2018, 1–10.
15. Pleba M.: E-learning Tajniki edukacji na odległość. Wydawnictwo C.H. Beck, Warszawa 2011.
16. Pawlak P., Strzelecki W.: E-LEARNING A MEDYCYNA. Studia Informatica Zeszyty Naukowe Uniwersytetu Szczecińskiego, 2010, 25(605), 97–111.
17. Korzan D.: Ewolucja kształcenia zdalnego. [w:] Kształcenie ustawiczne – idee i doświadczenia. Kruszewski ZP., Półturzycki J., Wesołowska EA. (red.). Wydawnictwo Naukowe NOVUM, Płock, 2003, 383 – 401.
18. Meger Z.: Szósta generacja nauczania zdalnego. [w]: E-edukacja w rozwoju społeczeństwa. Dąbrowski M., Zając M. (red.). Fundacja Promocji i Akredytacji Kierunków Ekonomicznych, Warszawa, 2008.
19. Kuźmicz K.: E -edukacja jest wszędzie – rozważania dotyczące istoty i zastosowania technologii mobilnych w kształceniu zdalnym. [w:] Język @ multimedia: dialog – konflikt. Dytman-Stasieńko A., Stasieńko J. (red.). Wydawnictwo Naukowe Dolnośląskiej Szkoły Wyższej, Wrocław, 2012, 129–40.
20. Landowska A., Kaczmarek J.: WSPÓŁCZESNE TRENDY W DZIEDZINIE SYSTEMÓW ZDALNEGO NAUCZANIA. Zeszyty Naukowe Wydziału Elektrotechniki i Automatyki Politechniki Gdańskiej, 2004, (22), 111–116.
21. Marescaux J., Leroy J., Rubino F., Smith M., Vix M., Simone M., Mutter D.: Transcontinental robot-assisted remote telesurgery: Feasibility and potential applications. Annals of Surgery, 2002, 225(4), 487–492.
22. Masic I.: E-Learning as New Method of Medical Education. Acta Informatica Medica, 2008, 16(2), 102–17.
23. Al-Balas M., Al-Balas HI., Jaber HM., Obeidat K., Al-Balas H., Aborajooh EA., Al-Taher R., Al-Balas B.: Distance learning in clinical medical education amid COVID-19

pandemic in Jordan: Current situation, challenges, and perspectives. BMC Medical Education, 2020, 20(1), 341.

24. Memon AR., Rathore FA.: Moodle and online learning in Pakistani medical universities: An opportunity worth exploring in higher education and research. Journal of the Pakistan Medical Association, 2018, 68(7), 1076–8.
25. Kim KJ., Kim G.: Development of e-learning in medical education: 10 years' experience of Korean medical schools. Korean Journal of Medical Education, 2019, 31(3), 205–214.
26. Dhir SK., Verma D., Batta M., Mishra D.: E-learning in medical education in India. Indian Pediatrics. 2017, 54(10), 871–877.
27. Walsh S., De Villiers MR., Golakai VK.: Introducing an E-learning solution for medical education in Liberia. Annals of Global Health. 2018, 84(1), 190–197.

Functioning of the family of a patient with neoplastic disease

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Family and its role

As the most crucial educational element, the family is responsible for forming a person from an early age until death.

In the literature on the subject [1,2,3], the functions of the family are closely related to its structure. According to Tyszka [3], they are "a reflection of family life in various forms. For example, the foundations that regulate its life and how a given family is maintained or maintained are a multigenerational family or small family. In the modern family, after Ziemska [4], the function of meeting psychosocial needs comes to the fore.

Field [5] distinguishes five types of families: correct (based on a loving marriage, creating a harmonious whole, with sincere and open communication, resolving, in a manner respecting one's own and spouse's dignity, conflicts immediately after they arise); power (rules are put before interpersonal relations and feelings, it is dominated by strictness in relations, and its members often feel lonely); overprotective (parents live and devote themselves to their children, and their own needs and development fall into the background); chaotic (without bonds, with constant conflicts, brawls, and aggression) and entangled (parents use children to meet their own needs and very often one of the parents manipulates the children).

On the other hand, Kavula [6] distinguishes between a small family (nuclear - including children, parents, and sometimes grandparents living together and running a typical household) and large (including distant relatives, or at least relatives in a straight line up to the third generation).

Each family should behave by the family homeostasis strategy to maintain balance and stability in mutual relations. When this balance is threatened by destabilization, all family members should act in concert to preserve it. The importance of the role of the family increases more in the event of the disease of its member.

Disease and sickness phases

In the literature, following Bąk-Sosnowska [7], several ways are mentioned to react to an unsuccessful diagnosis/disease. It may be a denial of the diagnosis, diminishing (acknowledging the diagnosis but minimizing it, finding a rational explanation for the symptoms that appear), exaggerating (excessive concentration on symptoms, and acceptance of the diagnosis [7].

According to Kondaš [8] the patient's attitudes towards ill include rejecting and anxiety. In turn, Makselon [9] distinguishes three types of attitudes: accepting, imaginary, and hope (disposition for long-term recommendation in overcoming the disease, mobilization to be active).

In the experiences of the patient and the family, Kübler-Ross distinguishes several periods/phases after obtaining information about the disease [10]:

- denial and isolation - human defensive reaction, which over time may weaken and transform into an attempt to distort reality
- phase of anger - a sick person is full of irritability towards the family and medical staff for insufficient care,
- the third phase is bargaining, reflecting on the disease and one's surroundings, the tendency to take action in the hope that he will recover, for this purpose, e.g, he negotiates with a doctor and God, makes promises
- the fourth phase is depression - depressed mood, patients, cry, talk about suicide, are desperate, sad, feel useless, feel a significant loss, e.g., due to deformation of the body, guilt, reading the disease as a punishment for mistakes, the appearance of fatigue with illness, silence, unlimited sadness, isolation from the environment, not making contact with other patients

  the fifth and last phase - accepting fate and calmly accepting it; the sick person needs a lot of sleep, he is overwhelmed by resignation and hopelessness, but he is free from rebellion and depression. At this stage, the family often needs more support than the sick person.

The Kübler-Ross theory has had a significant impact on the mindsets of doctors, psychologists, nurses, and social workers, as well as patients and their families. In later studies by other authors, it turned out, however, that not all patients underwent the described five phases of adaptation to the death-threatening neoplastic disease [11, 12].

Taylor, in turn, proposed a different division of the processes taking place in the human psyche under the burden of cancer, the so-called theory of cognitive adaptation, according to which a person adapts to the threat of disease according to three phases [13]:

- searching for the meaning of the disease
- attempting to regain at least partial control over the threatening situation or the alleged cause of it;
- recovery of self-esteem, which is often done through the 'compare down' method.

Unfortunately, studies by other authors also did not confirm the universality of the phases of the cognitive adaptation model in patients with the severe somatic disease [14].

Currently, the situation of a cancer patient and, indirectly, his family is described by two theoretical models [14]:

- the psychological model of stress, proposed by Lazarus and Folkman - the basis for understanding the interaction between disease and the human body as a biopsychosocial unit,
- coping with the disease - understood as a dynamic process, consisting of specific strategies and individual style, understood as multidimensional and universal, and a particular form of adaptation to a stressful situation.

According to Kozak [15], dealing with cancer begins with noticing the first disturbing symptoms associated with making new decisions. Quick contact with the doctor is essential here, which can be different in practice. Sometimes how quickly this contact occurs depends on the interpretation of the symptoms, which may be disrespectful (e.g., bleeding or delaying to a doctor") [15].

A significant problem for the patient and his family is procrastination with diagnosis (the period between the first noticeable signs of the disease and the following medical consultation) [16]. In literature, [16], the following stages of procrastination are distinguished:

- appraisal delay - most of the time, delay in cancer diagnosis associated with the difficulty of assessing the severity of the observed symptoms and being able to cope with their consequences;
- illness delay - the number of days from a person declaring he or she is ill to the day he or she decides to seek medical attention
- behavioral delay - the number of days (months, years) between the decision to seek medical help and the moment of updating this decision by going to the doctor
- scheduling delay refers to taking personal action on medical advice obtained

The literature emphasizes that the stage of diagnosis of the disease (from noticing lesions to the time of reporting to the doctor, undertaking tests to confirm the presence of the tumor, making the diagnosis) is characterized by a significant disturbance of mental balance (anxiety, disorientation, anger appear), caused by a sense of threat, uncertainty about the future and anticipating the possibility of a bad prognosis) [15].

The experienced phase of acute distress usually ends after 7–14 days, when the patient's attention shifts to planning the treatment [16]. During this period, family members may have divergent thoughts - on the one hand, an attempt to understand the patient's fear and pain, and on the other, a desire to escape from the existing problems and the patient himself. Too much information obtained in this period may be the reason for overloading even the strongest and healthiest person [3]. There may be intrusive thoughts about one's mortality, obsessive thoughts about the need to regulate different life or financial matters [2].

The treatment stage is a very stressful period for the whole family. This a period of great tension, often manifested by difficulties in falling asleep, fatigue after waking up, uncertainty and unpredictability of the disease itself, especially therapy, but at the same time the time when hope for recovery and coping with the disease crisis appears [15].

During this period, the awareness of family members becomes more and more sensitive to the patient's needs. There is rapprochement and emotional support and accepting the patient's feelings, even those unacceptable. Occasionally, however, healthy family members may develop over-fusion with the patient, which a blurring of family boundaries may accompany. In turn, the patient may develop emotional lability (from pessimistic predictions to euphoric plans for the future). The caring family member must then be careful because the patient's optimism can often be easily quenched with an inappropriate word, behavior, or misunderstanding of the intention [1,2,3,4].

The so-called seemingly paradoxical anxiety may accompany the end of treatment because patients become worried about the lack of frequent visits to the doctor or less frequent monitoring of their Health. There is a fear of losing protection and safety, which gave them the previous treatment and the fear of the possibility of relapse [14].

The stage of disease remission is the recovery of the patient and family members to their former social roles [4, 17,18]. Quite often in the patient, there is the so-called Damocles syndrome, i.e., constant vigilance and self-control, obsessively recurring thoughts about cancer, persistent fear of relapse, increasing before the follow-up examination. However, after reevaluating his goals and aspirations, the recovered person often experiences a new joy in life. The patient becomes more active. Family members, in turn, are either accepting and supporting

or criticizing the patient, staff, friends, or other family members or forcing the patient to revert to pre-disease roles and behaviors fully. They may not accept the current state, avoid being alone with the healer, run away to work, or other out-of-home duties, and this may cause conflicts [4, 17,18].

To sum up, it should be emphasized that although the differentiation of the individual phases of the disease and the treatment process is of great clinical and therapeutic importance. It enables understanding the situation and the needs of the patient and his family. Cancer is a challenge that comes with patients' physical, psychological and social problems and their families.

The influence of the disease on the functioning of the family

The cancer experience is a state of deep psychological crisis, both for the patient and his family, which manifests itself in cognitive, behavioral, and emotional levels.

Cancer disrupts the functioning of the family, changes not only the patient's life but also the entire system. Whether its members will overcome the crisis and move to the next stage depends on whether they will accept the changes taking place and whether they will create realistic attitudes [19]. Regardless of the patient's age, the disease is an existential experience of particular importance for the entire family system. It causes changes in all family members' thinking, goals, values, mood, activity, and mental state. However, these specific changes depending on the phase of the disease and its treatment [20].

The American psychologist Allport defined a crisis as "situations of emotional and mental stress that require a change of perspective but quickly. Importantly, these changes in perspective entail changes in the personality structure, which in turn can be progressive or regressive" [21]. The above definition specifies that a person in a state of crisis cannot use the current coping methods with stress under the influence of a traumatic event. These methods become ineffective, insufficient, and ineffective. This situation leads to the development of new adaptive methods [22, 23],

The mental crisis of a person who has cancer and his family, also experiencing it, is characterized by specific dynamics and stages [22,23]. Each of the successive stages allows you to adapt to a new situation, and at each level, you can distinguish individual reactions depending on the defense mechanisms used. They can be defined as an unconscious mental

activity involving experience and action. Defense mechanisms are common to all people; they do not depend on age, gender, or health condition. Their role is to maintain a sense of security and falsify the image of the surrounding reality and themselves. The primary purpose of the existence of defense mechanisms is to avoid mental pain, reduce the intensity of unpleasant feelings, and maintain self-esteem [22,23].

A characteristic feature of a family with cancer is the increase in cohesion and closeness, increasing emotional distance to people outside the family environment [24, 25].

Families struggling with cancer show limited communication, suppressing emotional animosities and conflicts during a disease crisis. Confrontations are avoided. Once you accept all the cunning changes and address them appropriately, family communication can be enriched, and the whole family can come closer together. The whole family's attention is focused on the sick person, who becomes the most important entity in the family. The family's strength is on maintaining homeostasis; however, even a single change may increase instability and cause an additional psychological burden to the whole family [26, 27].

All forms of family reorganization are carried out to cope with the new situation [22, 28]. The changes cover all fields of family functioning, both in the emotional, socialization, and material-securing dimensions. Unfortunately, overload and excess of duties accumulate, burdensome fatigue and lack of time to rest, and the professional responsibilities performed so far are disturbed, or a decision is made to resign from work [29].

Regardless of when the family learns about the cancer of a family member, such information evokes in all its [30] members: fear, fear, shock, guilt, rebellion and anger directed at oneself, God and the medical staff, despair and helplessness that could lead to depressive withdrawal from any activity and resulting in surrendering to the course of events. The effect of strong stressors and the lack of effective compensation mechanisms may result in the development of post-traumatic stress disorder [31, 32].

Depression and distress are other severe mental and diseased mental injuries. Cancer distress is an "unpleasant psychological, social, and spiritual experience" and can vary in severity and severity throughout the treatment process. In healthy family members, the diagnosis of depression should be based on the classic principles of diagnosing this disease entity. In contrast, in the case of a patient, the diagnosis should be based primarily on psychological symptoms, i.e., low mood, loss of self-esteem, the emergence of a sense of hopelessness, helplessness, worthlessness, and anhedonia [31, 32].

Two types of changes can occur in families with cancer [20, 33]:

- The first type is related to the increased need for experiencing cohesion/closeness, the disappearance of spatial, temporal, and barriers between family members, increasing their emotional distance to people from outside and those outside the family environment
- The second type may be associated with demonstrating hostility, rejecting the sick person, dividing families, maintaining only good external relationships (keeping the appearance that everything is ok), breaking up families, increasing the feeling of insecurity, and additional burdens the family.

According to Taranowicz [34], how the family deals with the situation depends on the resources at its disposal, including:

- material (income, housing conditions), cultural (knowledge, skills, behavior patterns, system of values and norms)
- time (time devoted directly to a disabled person, without prejudice to other areas of activity)
- human (family size, age of family members, their health and fitness)
- ability to support social support.

The diagnosis of cancer in one of the partners, especially when the sick partner enters the period requiring palliative care, may cause an intense crisis, especially in married couples with a short period of service [35].

Young partners are not fully consolidated and separated from their parents. In such cases, it is more likely that the marriage will break up and return to dependence on parents, siblings, with the separation or exclusion of a healthy partner. There may also be a conflict between partners and their parents. Therefore, delicacy, tact, and wisdom are required on the family, especially parents. On the other hand, in families with a more extended experience, family problems may be somatic and psychological. Patients may hide their issues in the form of indifference or lack of affection towards their partner, so partners must learn tact, delicacy, and mutual understanding. At the beginning of the disease, try to adjust the lifestyle to the sick person's needs, and in the chronic period to an increasing extent, take into account one's needs [35].

Attempts to repair family relationships (planning new purchases, having children, career development) are often undertaken in periods of cancer remission or rehabilitation, but unfortunately, may be marked by the already mentioned "Damocles sword syndrome" [20, 35].

Unfortunately, in this family of patients, fear of relapse, sexual disorders, decreased self-esteem, depressive disorders, and even suicidal thoughts may appear, which requires support from relatives and psychological help [20, 35].

It happens that, despite the oncological treatment, the disease does not give up; it returns. Then in the family, the struggle for the patient and her previous experiences begin anew [20, 35],

Even more significant changes occur in the family than before, usually negative ones, concerning materials, emotional and communication problems, and relations with extended family, friends, acquaintances, and neighbors. The stability of the family system may also break down, depression, anxiety, suicidal thoughts, resignation from social roles, and emotional burnout may develop [20, 35]

Family members often feel loneliness, a sense of loss, fear of the patient's death, and concern for him to suffer as little as possible. In some families, the first talks about death take place at this stage [20].

The disease enters the terminal period, causes another breakdown of the stability of the family system, the necessity to say goodbye to the dying person before talking about death and mourning to the members. The family is accompanied by loneliness, a sense of loss, fear of the patient's death, and concern for him to suffer as little as possible. In some families, the first talks about death take place in this phase [20, 25, 35]

The period of mourning and the possibility of releasing the pain after the loss are no less difficult. Without it, none of the family members will be ready to come out of the void after death [36].

The influence of neoplastic disease on the functioning of children in the family

A population study by Huizing et al. [37,38] showed that about 2.8 million children live in the USA with parents diagnosed with cancer. This fact justifies the purposefulness of paying special attention to children in families with cancer disease. Parent's illness may create educational problems and aggressive behavior [35].

Such a child should be provided with care, interest, and contact with peers because confronting a severe illness of a family member may lead to temporary or permanent changes in the life of children [35].

Research by Kennedy et al. [39] has shown that even young children (under 7) try to find information about a parent's disease in various sources (leaflets, books, the Internet). Huizing et al. [37, 38] that children in on average 11 years of age are already well-informed

about the disease in the family and its consequences.

Children experience various difficulties depending on the phase of the disease of a family member [20, 24, 35, 40, 41]:

- during the diagnosis phase, they are usually isolated from bad news, but even if they do not know about the disease, they may feel tense and anxious, especially when the parents do not have time to provide detailed explanations to the child. They may feel rejected, and as a result, feel loneliness, weakened relationships with their parents, and even destructive behavior. Children have weaker contact with medical staff; hence they know less about the parent's disease, which also causes additional problems in adapting to new conditions.
- during the treatment phase, they may notice both physical and emotional changes in the parent. They experience anxiety, a sense of guilt for the disease, mood changes, and feel anger for being abandoned, especially by a sick person, and moments immediately after surgery are particularly stressful situations, after chemotherapy or radiotherapy.
- in the remission phase of the disease, the child feels great joy, hopes that everything will return to normal, that he will be able to take care of his affairs, returns to his group of friends
- at the end of life, it is essential to prepare the child for the death of the parent, as he feels that the situation is bad, but the child's age must be taken into account in this respect, which determines the possibility of understanding death.

The child's approach to the disease in the family is also affected by the child's age [20,35]:

- in families with young children, the development of cancer may result in the loss of the ability to assume the role of a parent
- in families with adolescents, there are psychosocial development of a teenager, may rebel against the situation in the family, treat it as injustice and reject even a sick one
- In adult children, cancer may also stop them from leaving the family system and delay the developmental tasks of young people who need to become carers and helpers for aging parents.

The studies conducted in children from 4 to 11 years of age from families with cancer have shown that children may be more emotionally stimulating [41]. A may have more somatic disorders [42], and on the other hand, that such children function better than their peers from

families not burdened with disease [41].

On the other hand, in the case of adolescents, somatic symptoms appear more often (headaches, abdominal pain, lack of appetite, difficulty falling asleep), and social functioning usually does not differ from the disease presented by adolescents from families without the disease [41, 42].

On the other hand, research by Wong et al. [43] showed that almost half of adolescents having a parent with cancer experienced in some aspect greater recognition of life, positive changes in health behavior, or more intimacy in social relationships.

It has also been shown that the daughters of people who have cancer have greater emotional problems than the sons [38] and that the most significant psychological problems were experienced by the children in the case of the mother's disease [44].

The functioning of children of families with cancer is also influenced by marital satisfaction and positive family relationships - the better they are, the better the children endure the new situation [43].

However, the parent's illness is also an opportunity to teach the child to care for the dying person, pass on positive models to him, and transfer to his relationships with relatives in the future [20, 35].

The role and functions of social support

The disease and the resulting hospitalizations result in limitations in the patient's current lifestyle [45]. In the opinion of Deręgowska [45], the hospital environment hinders the patient every day, making him completely subordinated to the decisions of medical staff, and the stress resulting from the presence of the disease is exacerbated by hospital stress. Therefore, a patient treated for a neoplastic disease requires comprehensive rehabilitation, including somatic and mental areas, to support the patient [45].

Working through the problem of the disease and the related requirements can only be achieved through a long and multi-stage mental process, the so-called coping process. This process should be understood as "*cognitive, emotional and behavioral actions undertaken by both the individual and the whole family to meet all the demands of the disease and the treatment process*" [47].

It occurs both during and after treatment, but for it to proceed as smoothly as possible, it is necessary to support the patient and his family [47]. When cancer is diagnosed, the need

for social support grows suddenly [47, 48].

The Medallion care model [49], assuming that the patient's family has several tasks to perform, such as:

- emotional support of the patient
- adaptation to the range of therapeutic actions that need to be performed in combating the disease or its effects.
- understanding by other family members of the disease
- learning how to prevent flare-ups of disease symptoms - relapses
- maintaining and carefully cultivating, as much as possible, customs, holidays, and family rituals, if possible, with the participation of people from outside the strict family system, so that the patient does not feel rejected
- the ability to engage external influences when needed and the accompanying ability to transform one's internal structure.

Providing support should have a positive impact on removing the problem as quickly as possible. It should prepare the supported person to deal with similar situations independently in the future [49, 50]. However, it cannot be forgotten that the essential elements of adequate support are the helper's skills and personality.

Such a person should be empathetic, aware of his system of values, clear ethical principles, interest in social matters, and a sense of responsibility for others. The ability to listen to the other person and establish interpersonal contacts is also invaluable [47, 48].

Social support is defined as resources that are provided to an individual through interactions with other people. The aim is to reduce stress or psychological crisis by exchanging emotions, accompaniment, a sense of security, hope, a sense of belonging, and bringing closer overcoming the crisis and solving existing problems [50, 51].

Providing support to patients and their families should start as soon as possible [52]. A friendly atmosphere should be created around them, full of trust, conducive to establishing relationships and making difficult decisions. A perfect relationship includes an attitude of respect, honesty, and cooperation of the entire medical team, positively impacting the other elements of therapeutic management during medical and nursing interventions [52, 53].

The beneficial relationship between coping with complex (crisis) situations and social support is explained by two models [54, 55]:

- main effect model - describes the importance of ties, relationships, and social networks. According to its assumptions, the very belonging to a specific social structure increases

the level of the quality of life and is also a source of a sense of stability, predictability, positive experiences, emotions and fosters a sense of security.

- the buffer model defines the role of support as a buffer against the destructive consequences of stress. It causes a change in beliefs about one's skills, an increase in awareness of one's abilities, and beliefs about one's effectiveness.

Langford et al. [56] and Hupcey [57] distinguish several types of support:

- structural - defined as an objectively existing social network in the environment of an individual, consisting of informal and possible sources of help, in which the person or persons who are potential recipients of support is embedded, constituting the basis through which the support process may take place
- functional - refers to the function and quality of social interaction in which at least two people participate. The support process takes place, that is, the transferor exchange of various types of resources. support process
- instrumental - consisting in providing information or instructions on specific ways of proceeding in a particular situation
- emotional - soothing negative feelings, releasing a sense of hope, improving self-esteem and well-being
- informational - allowing for a better understanding and assessment of a crisis
  material - being specific material and financial aid
- spiritual - relating to the sphere of meaning and spirit, relieving suffering and pain associated with, for example, illness
- perceived - being the beliefs of the individual regarding the availability of support
- received - measured objectively or estimated based on the relationship of the person to whom it is directed.

Kahn and Antonucci, following Pommersbach [58], divide supportive behavior into three groups:

- expressing caring and emotional closeness
- providing information on the correctness of the actions taken
- availability of time, effort, and money assistance.

Wills, after Pommersbach [58], distinguishes between support:

- supporting self-esteem - comparable to emotional support because the presence of close people and experiencing acceptance counteracts the adverse effects of stress, and maintaining self-esteem is one of the functions of social support

- prestigious - because the supporting properties of social bonds may result from the very fact of their existence

  informational - providing information, advice, and expressing judgment in conflict situations
- instrumental - providing help in solving complex life tasks, may take the form of borrowing money or goods
- social intercourse is one of the forms of coping with stress through participation in various forms of social life, e.g., concerts, meetings, going to the cinema, theater, and participation in tourist and sports events.
- motivational - it is of particular importance for people who find themselves in a difficult situation, which has a chronic form; it encourages and motivates the subject to persevere in efforts to eliminate the problem or improve their condition significantly.

According to Kawula [6], there are five levels of social support, which can be one-sided or two-sided and permanent or changeable: emotional, evaluative, instrumental, informative, and spiritual

Therefore, for example, social support seems to take place in various situations and phases of human life, and activities supporting it in four basic systems [6]:

- human-human (family, peer, neighborly, professional, friends relationships)
- human-group (own family, associations, neighborhood and local environments, churches, sub-cultural groups, support groups)
- people - institutions (institutions of assistance and legal, medical and social advice, service and educational institutions, institutions of broadly understood social policy, local government and self-help institutions)
- human - broader systems (including relations of the commune, city or its district, the region of residence, ethnic and cultural region, regional, national, and international organizations and associations).

Kawczyńska-Butrym [59] mentions information, emotional, material (material and financial) support, and the provision of services and development that concerns children and may initially shape psychomotor skills and then in focusing interests and equalizing educational opportunities.

On the other hand, Karwowska [60] distinguishes preventive and educational, compensatory, psychological and pedagogical, rescue, informative and spiritual as well as professional (doctors, psychologists, lawyers, etc.), non-professional (provided as part of

informal assistance), self-help support (groups of parents of children with based on support groups) and through volunteering.

Maciarz [61] describes psychoemotional support, care and educational support, social support, and rehabilitation support.

In the environment of the patient and his family, there are generally specific groups of social support, such as family, friends, acquaintances, teachers, clergy, doctors, nurses [47].

Natural reference groups should first provide support, i.e., family, friends, neighbors, peers. Still, it is also essential that people in need have the opportunity to benefit from professional help provided by both governmental and local government institutions and medical professionals, with whom the family and the patient have constant contact during the treatment process [46, 62, 63].

Currently, most oncology departments offer psychologists who support challenging moments of conveying the news about cancer diagnosis and being a support during a crisis or a moment of doubt. Non-profit institutions established by civil society in associations, foundations, support groups, or self-help groups also play an increasingly important role. Each group mentioned may focus on providing a different type of support in the psychoemotional or social-service field [50, 62, 63].

Conclusions

There is no routine psychological care in modern care for patients with oncological problems, especially for children. However, psychological intervention can significantly help the patient and his family and the entire medical team be better involved in the treatment process. As a rule, it is assumed that a sick person experiences the most changes in functioning in chronic disease, and the family, which is also "ill" together, is forgotten. The lack of psychological and educational counseling and support from oncological institutions concerns various areas, especially fighting the disease or the ability to talk to children about their disease. After being diagnosed with a cancer problem in a family member, young family members should immediately undergo intervention to reduce the impact of stressful situations. Such help plays an essential role in providing support and strengthening in coping with a chronic disease situation.

References

1. De Barbaro B. Introduction to the systemic understanding of the family, Publishing House of the Jagiellonian University, 1999. (Polish)
2. Tyszka Zb, Wachowiak A. Basic concepts and issues of family sociology, Wyd. Agricultural Academy August Cieszkowski, Poznań, 1997. (Polish)
3. Tyszka Z. Family sociology, PWN, Warsaw, 1976. (Polish)
4. Ziemska M. Family and personality. PWN, Warsaw, 1975. (Polish)
5. Field D. Family Personalities, Wyd. Logos, Warsaw, 2007. (Polish)
6. Kawula S. Social support [in:] Elementary concepts of social pedagogy and social work, Lalak D, Pilch T. (ed.), Wyd. Academic "Żak", Warsaw, 1999, 338. (Polish)
7. Bąk-Sosnowska M.Illness in human life [in:] Psychology. A textbook for medical students, Trzcieniecka-Green A. (ed.), TAiWPN Universitas, 2006, Kraków, 172 - 228. (Polish)
8. Kondaš O. Clinical psychology. PWN, Warsaw 1984. (Polish)
9. Makselon J. Psychological aspects of suffering. Sympozjum, 2000; 4/2(7):71-83.
10. Kübler-Ross E. Kübler-Ross E. Conversations about death and dying, Wyd. Media Rodzina, 1st Polish edition, Poznań 1979. (Polish)
11. Liss-Levinson W.S. Reality perspectives for psychological services in a hospice program. American Psychologist, 1982; 37(11): 1266–1270. https://doi.org/10.1037/0003-066X.37.11.1266
12. Schulz R, Aderman D. Clinical research and the stages of dying. Omega 1974; 5: 137–143.
13. Taylor SE. Health psychology. New York: McGraw-Hill; 2003.
14. Jabłoński M, Furgał M, Dudek D, Zięba A. The position of psychooncology in contemporary psychiatry. Polish Psychiatry, 2008; 42(5): 749–765. (Polish)
15. Kozaka J. The clinical course of cancer and mental adjustment. Current Gynecologic Oncology 2015; 15: 27-43. https://doi.org/10.15557/CGO.2015.0004;
16. Kozak S. Social orphanage: psychological analysis of disturbances in the behavior of children from orphanages. PWN, Warsaw, 1986. (Polish)
17. Pawełczak M, Pilarczyk J, Pobudejska-Pieniążek A, Wojtasik N. Anxiety in families of children with cancer. Psycho-Oncology 2012; 2: 29-36.

18. Stolarska M. Dylematy medyczno-etyczne w opiece nad dziećmi z chorobą nowotworową. Medical and ethical dilemmas in caring for children with cancer. Opieka Paliatywna nad dziećmi, Palliative care for children 2008; 16: 25-28.
19. Kruk-Zagajewska A, Kuśnierkiewicz M, Szmeja Z, Golisiński W. Postawy rodzin wobec chorych onkologicznie. Families' attitudes towards oncological patients Psycho-Oncology . 1997; 1, 47–50. (Polish)
20. Pietrzyk A. This disease in the family. A psychologist about cancer. Impuls Publishing House, Krakow 2006. (Polish)
21. Płużek Z. Pastoral psychology. ITKM Publishing House, Krakow 2002.
22. Mikuła R, Lipiec S. Selected issues of psychiatric and psychological care in cancer patients. [in:] Multiple myeloma. Volume II - selected issues. Skotnicki A, Jurczyszyn A. (eds.). Górnicki Medical Publishing House, Krakow 2011: 185-214.
23. Stolińska-Pobralska N. Hospice for Children as a Institution Supporting Family in Crisis. Pedagogika Rodziny Pedagogy Family 2012; 2/1: 112-123.
24. Rogiewicz M. Psychological problems of children and adolescents. In: Psychooncology. de Walden-Gałuszko K. (ed.). Library of Polish Psychiatry, Krakow 2000: 101-116. (Polish)
25. Babcock E. When life becomes precious. Hunter House. Alameda 1997.
26. Stenka K, Izdebski P. Parents facing their child's struggle with cancer. Journal of Psychiatry and Clinicl Psychology, 2018; 18: 306-314. https://doi.org/10.15557/PiPK.2018.0038
27. Zielazny P, Zarzeczna-Baran M, Wojtecka A. System rodzinny a nowotwór - wybrane zagadnienia. Medycyna Ogólna i Nauki o Zdrowiu Family system and cancer - selected issues. General Medicine and Health Sciences 2013; 19: 439-444. (Polish)
28. Pilarczyk J. Rola psychoonkologii w leczeniu chorób nowotworowych u dzieci. [w:] Psychologia w naukach medycznych. Cybulski M, Strzelecki W. Wydawnictwo Naukowe Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu, Poznań, 2011: 44-55. The role of psycho-oncology in the treatment of neoplastic diseases in children. [in:] Psychology in medical science. Cybulski M, Strzelecki W. Scientific Publishers of the Medical University of Karol Marcinkowski in Poznań, Poznań, 2011: 44-55
29. Baruch A. Child's cancer as a factor causing changes in the functioning of the family - selected aspects Przegląd Pedagogiczny Pedagogical Review 2013; 2: 133- 148.

30. Cepuch G, Dębska G, Foryś Z . Family in a situation marked by a disease that threatens the child's life. [in:] The family in health and disease: selected aspects of care for the chronically ill. Dębska G, Goździalska A, Jaśkiewicz J. (eds.). printing house Academia Modreviana Cracoviensis Andrzej Frycz Modrzewski Krakow University. (Polish)
31. Kuty-Pachecka M, Stefańska K. Mental disorders in children diagnosed with cancer. Journal of Psychiatry of Psychology, 2014; 14: 156-163. https://doi.org/10.15557/PiPK.2014.0024
32. Kieszkowska-Grudny A. Distress and depression in cancer patients – diagnosis and treatment. OnkoReview 2012; 2: 246-252.
33. Wirsching M. Around cancer. Gdańsk Psychological Publishing House. Gdansk 1994
34. Taranowicz I . Family and the problems of Health and disease [in:] Health and disease. Selected problems of medical sociology, Barański J, Piątkowski W. (ed.), Wrocław, 2002, 2002, 105-115.
35. de Walden - Gałuszko K, Psychooncology in clinical practice. PZWL Medical Publishing, Warsaw 2011.
36. Alexander H. The experience of mourning. Publisher On the way. Poznań 2001.
37. Huizinga G A, Visser A, Zelders-Steyn E, Teule A, Reijneveld S.A, Roodbot PF. Psychological impact of having a parent with cancer. Europ Cancer. 2011; 47(3): 239–246.https://doi.org/10.1016/S0959-8049(11)70170-8
38. Huizinga GA, Visser A, van der Graaf WT, Hoekstra HJ, Stewart RE, Hoekstra-Weebers JEHM. Family-oriented multilevel study on the psychological functioning of adolescent children having a mother with cancer. Psychooncology 2011; 20(7):730-737. https://doi.org/10.1002/pon.1779.
39. Kennedy VL, Lloyd-Williams M. Information and communication when a parent has advanced cancer. J Affect Disord 2009; 114 (1−3), 149−155. https://doi.org/10.1016/j.jad.2008.06.022
40. Davey MP, Tubbs CY, Kissil K, Nino A. 'We are survivors too': African- American youths' experiences of coping with parental breast cancer. Psychooncology 2011; 20 (1), 77−87. https://doi.org/10.1002/pon.1712
41. Visser A, Huizinga GA, Hoekstra HJ, van der Graaf WT, Hoekstra- -Weebers JE. Temperament as a predictor of internalising and externalising problems in adolescent children of parents diagnosed with cancer. Support Care Cancer 2007; 30; 15, 395–403. https://doi.org/10.1007/s00520-006-0117-7

42. Osborn T. The psychosocial impact of parental cancer on children and adolescents: a systematic review. Psychooncology 2007, 16(2), 101−26. https://doi.org/10.1002/pon.1113
43. Wong ML, Cavanaugh CE, Macleamy JB, Sojourner-Nelson A, Koopman C. Posttraumatic growth and adverse long-term effects of parental cancer in children. Fam Syst Health 2009, 27 (1), 53−63. https://doi.org/10.1037/a0014771
44. Flahault C, Sultan S. On being a child of an ill parent: A Rorschach investigation of adaptation to parental cancer compared to other illnesses. Rorschachiana 2010; 34, 43−69. https://doi.org/10.1027/1192-5604/a000004
45. Deręgowska J. Education of children and youth with cancerous disease as a support factor. Educational studies. 2012; 21: 279-298.
46. Hesselbarth B, Graubner U. Hesselbarth B, Graubner U . Psycho-oncology in paediatrics. [in:] Psychooncology. Diagnostics - therapeutic methods. Dorfmüller M, Dietzfelbinger H. (eds.). Elsevier Urban & Partner, Wrocław 2011: 269-279. (Polish)
47. Krzesińska-Żach B . Forms of supporting a sick child on the example of the Children's Teaching Hospital in Białystok. [in:] Child education - facts and myths. Trans Humana University Publishing House, Białystok 2010: 632-637. (Polish)
48. Zagozda M, Litwiniuk M, Ziarko M. Cancer relapse – emotional consequences and possibilities of psychological help. Letters in Oncology Science 2017; 14: 125-132. https://doi.org/10.21641/los.14.4.65
49. Medalie J, H. The patient and family adjustment to chronic disease in the home. Disabil. Rehabil, 1997, 19, 163-170. https://doi.org/10.3109/09638289709166523.
50. Budziszewska B, Piusińska-Macoch R, Sułek K, Stępień A. Psychological problems of the Family of the patients with haematological malignancies in the system theory. Acta Hematologica Polonica 2005; 3: 317-325.
51. Walter N. Social support and the critical situation in human life. [in:] Online social support. Socio-pedagogical study. Walter N.(ed) UAM Scientific Publishing House, Poznań, 2016: 41-62.
52. Wieczerzak K, Krzyżanowski D. Chosen Psychological Aspects of Quality of Life of Children with Blood Cancer. Nursing and Public Health 2011; 1: 129-134.
53. Konieczna I. Self-perception of children with chronic. Pedagogical Forum 2016; 1: 233-246. https://doi.org/10.21697/fp.2016.1.16

54. Chrapek E. Psychological difficulties, social support and stress management in parents of children with cancer. Journal of Psychiatry of Psychology, 2016; 16: 27-32. https://doi.org/10.15557/PiPK.2016.0005
55. Samardakiewicz M, Kowalczyk J. Psychooncological care over adolescentand young adult hematological patient. Hematology 2011; 2: 51-56.
56. Langford C.P, Bowsher J, Maloney J.P, Lillis P.P. Social support: a conceptual analysis. J. Adv. Nurs, 1997, 25, 95-100. https://doi.org/10.1046/j.1365-2648.1997.1997025095.x
57. Hupcey J.E. Clarifying the social support theory-research linkage. J. Adv. Nurs, 1998, 27, 1231-1241 https://doi.org/10.1046/j.1365-2648.1998.01231.x
58. Pommersbach J. Social support and disease The Review of psychology, 1988, 31, 503–525.
59. Kawczyńska-Butrym Z . Disability - specificity of social assistance. Ed. Silesia, Katowice, 1998. (Polish)
60. Karwowska M . Supporting the family of a mentally disabled child (in the context of social changes), printing house Impuls, Kraków, 2003
61. Maciarz A. Supporting the family in the upbringing and rehabilitation of children. Childhood Care and Education1992, 5/6, 254-257 (Polish)
62. Kózka M . Social support in disease. [in:] Models of nursing care for sick adults. Płaszewska-Żywko L, Kózka M. (eds.). PZWL Medical Publishing, Warsaw 2010: 45-49. (Polish)
63. Pacian A, Kulik T.B, Skórzyńska H, Ferenc W. Support role in cancer pain. Palliative Medicine, 2014; 6: 95-100.
64. Rauch PK, Muriel AC. The importance of parenting concerns among patients with cancer. Crit Rev Oncol Hematol 2004; 49(1): 37−42. https://doi.org/10.1016/S1040-8428(03)00095-7

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