

Review

By Prof. Zlatka Dimitrova Dimitrova, D.Sci, Head of ESL on Social Pharmacy at Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at SU "St. Kliment Ohridski"-Sofia, appointed as a Member of the Scientific Jury by Order No. RD-38-593/24.10.2023 of the Rector of the "St. Kliment Ohridski" Prof. D.Sci. A. Gerdzhikov.

Subject: procedure for the defense of a dissertation on the topic: "**Analysis of the diagnostic and therapeutic strategies in patients with arterial hypertension by the methods of measuring drug usability and rational drug use at the macro level in Bulgaria**" for the award of the educational and scientific degree "doctor" " by **Stefka Stoyanova Stoyanova**, Master of Pharmacy, full-time doctoral student at the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy in the field of Higher Education 7. Healthcare and Sports, Professional Field 7.3 Pharmacy, under the PhD program "Social Medicine and Organization of Healthcare and Pharmacy" with supervisor Prof. Emil Ivanov Hristov, MD, Ph.D.

This review has been prepared in accordance with the requirements of Law on the Development of the Academic Staff in the Republic of Bulgaria /LDASRB/, Regulations for application of the Law for the development of the academic staff in the Republic of Bulgaria/RALDASRB/ and the new Regulations on the terms and conditions for acquiring scientific degrees and occupying academic positions at SU "St. Kliment Ohridski", Chapter II. Acquisition of the ESD "Doctor" and the scientific degree "Doctor of Sciences", Section III. Conditions and procedure for acquiring the ESD "Doctor", as well as on the basis of my designation as a reviewer(protocol № 1 / 12.04.2023)

Procedure data. By Order №-PD-20-937/9.07.2020 mag. pharm. Stefka Stoyanova Stoyanova is enrolled as a full-time doctoral student in the field of higher education 7. Health care and sports, Professional direction 7.3 Pharmacy, in the doctoral program "Social medicine and organization of health care and pharmacy" in the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at SU "St. Kliment Ohridski", considered from 10.07.2020 to 10.07.2023.

The doctoral student's report on performance of the educational and scientific plan for the time of the regular doctoral studies was presented, as well as Order No. PД-20-1284 /25.07.2023 for her deduction due to the expiration of the deadline with the right to defend her dissertation after its discussion by the Department council and a decision on her readiness to be referred for public defense. The doctoral student's document folder contains all required documents for the defense of a dissertation.

At the first meeting of the Scientific Jury, which was held on 7.11.2023 at 2 p.m. were elected: chairman of the scientific jury - prof. Zlatka Dimitrova and two reviewers: Prof. Zlatka Dimitrova, DSci and Prof. MD Ivan Gruev, PhD/external member of the Scientific Jury/, and the other members of the Scientific Jury should submit opinions. The deadline for submitting reviews and opinions is 05/12/2023. Based on the submitted documents, incl. the certificate of fulfillment of the minimum requirements, the Scientific Jury decided to admit the candidate to the evaluation and set a date for the public defense December 21, 2023 at 2 p.m. in the Faculty of Chemistry and Pharmacy ,room 501.

Biographical data and career development of the candidate: M. Pharm. Stefka Stoyanova Stoyanova was born on 21.02.1995 in the city of Yambol. She graduated and obtained a master's degree in pharmacy in November 2019 at the FChPh at SU-Sofia with an excellent 5.75 in the studies and an excellent 6 in the state exams. After graduation, she started working as a master pharmacist in "Multipharm Prima" EOOD, Yambol, Sanita^s pharmacy - Krasimira Shunina LTD, Copharmacy 34 LTD, Sofia, from 18.04.2023 - in PharmAdvice LTD, Sofia and from 16.10.2023 after a competition and selection was held as an assistant professor at ESL on Social Pharmacy in the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy , "St. Kliment Ohridski" University. As a full-time doctoral student, she conducts practical classes with pharmacy students on pharmacoconomics and social pharmacy. During the period 6.2016 - 05.2019 and 6.2022. – 06.2023 she was a member of the Faculty

Council at the Faculty of Chemistry and Pharmacy at Sofia University. During the period 2.2017 - 05.2019 she was the Chairman of the Student Council at the Faculty of Chemistry and Pharmacy and from 07.2021 - 08.2023 she was an external expert for the Health Technology Assessment Commission at the National Pricing and Reimbursement Council. She is fluent in written and spoken English and Russian.

Relevance and significance of the dissertation work. Arterial hypertension is a socially significant disease that affects over 1 billion people worldwide and is among the most common causes of death. In the United States, more than 20% of the population has arterial hypertension, with mean systolic pressure being higher in young men and in women over 60 years of age. 65% of patients with AH are over 60 years old. In Europe, 30-45% of the population suffer from AH. A slight decrease in the burden of the disease has been observed in Western Europe. In Bulgaria, on average, about 2 million people are hypertensive. According to data from Eurostat for 2017, Bulgaria is in first place in terms of deaths caused by diseases of the circulatory organs (COD) - 66.4%, and cardiovascular diseases are among the main causes of death - for Bulgaria it is about 56% of cases and according to this indicator, our country is in first place in the European Union. I believe that the dissertation work of mag. pharm. Stefka Stoyanova Stoyanova, a full-time doctoral student in the doctoral program "Social medicine and organization of health care and pharmacy" has a significant and current topic from a scientific and practical point of view, as she analyzes and evaluates the availability, accessibility and drug usability in the treatment of uncomplicated essential arterial hypertension in Bulgaria through the use of quantitative and qualitative measures at the national level.

The dissertation submitted for review has a volume of 124 pages and is illustrated with 19 tables and 46 figures. The bibliography includes 189 sources, of which 56 are in Cyrillic and 133 in Latin.

Characteristic of the candidate's research and applied scientific activity.

The dissertation was discussed, accepted and referred for defense by the department council of the Department of Physical chemistry at the Faculty of Chemistry and Pharmacy, SU "St. Kliment Ohridski". It is structured according to the requirements and written in clear, professional and accessible language. The literature review is presented in 3 parts: in the first part, an analysis of the health problem arterial hypertension was carried out, including definition, history of the disease and the drugs used for its treatment, classification of the types of hypertension and the stages of hypertension according to blood pressure levels, risk factors that increase the probability of occurrence of the disease, the pathoanatomical changes and the affected systems and organs in case of incorrect treatment and complications - heart, brain, kidneys, blood vessels, hypertensive retinopathy, etc., the clinical picture and epidemiological data on the prevalence of hypertension in the world, USA, Europe, incl. and Bulgaria. In the second part of the literature review, non-pharmacotherapeutic and therapeutic approaches to the treatment of the socially significant disease arterial hypertension are described. Non-drug therapy refers to: lifestyle changes, salt restriction, moderate alcohol consumption, intake of a greater amount of fruits and vegetables, maintaining a normal body weight, stopping smoking, as well as regular physical activity. Depending on the severity of the hypertensive disease, the pharmacotherapeutic approaches are different. The main five classes of drugs used to control arterial pressure are considered - ACE-inhibitors, ARBs, beta-blockers, calcium antagonists and diuretics. Accordingly, each of these classes of medicinal products have specific indications and contraindications, which are always taken into account when preparing the individual therapeutic regimen of each patient with arterial hypertension. Algorithms are presented for the treatment of patients with uncomplicated AH, with AH and coronary artery disease, with AH and chronic renal failure, with AH and heart failure with reduced ejection fraction, with AH and atrial fibrillation. A comparative analysis of the Behavioral Guidelines for AH, editions of the European Society of Hypertension and the European Society of Cardiology in 2013 and 2018, which were applied during the period of the data used in the dissertation - 2017-2021, was performed. In the 2018 updated version of the guideline, treatment thresholds are different depending on the target patient population. It emphasizes more serious monitoring -

measurement of blood pressure also at home. In addition, treatment strategies should aim to prescribe combination therapies, in as few dosage forms as possible, with the aim of adherence to treatment, which is key to improving the health status of hypertensive patients. The role of both the prescriber and the dispenser of medicinal products is also outlined. Physicians and pharmacists should collaborate to monitor the results of the therapy of their hypertensive patients and encourage them to adhere strictly to their prescribed therapeutic regimen. In the third part of the review, a retrospective systematic review of scientific publications on the topic and keywords of the dissertation work for the period January 1990-October 2020 was carried out. Out of a total of 154 scientific publications found over the 30-year period, only 3 articles meet the set criteria, i.e. there is a lack of scientific publications on the epidemiology and treatment of uncomplicated essential arterial hypertension, both nationally and internationally, therefore we can claim that the chosen topic of the dissertation is poorly researched and its development will enrich scientific knowledge in this area. The overview clearly shows the good professional awareness of the doctoral student on the discussed issues. A good knowledge of the unresolved problems determine the purpose and tasks of her dissertation work. They are well substantiated and an adequate methodology has been chosen for the realization of the research.

The doctoral student sets herself a significant goal: "to perform an analysis of drug usability in the treatment of uncomplicated essential arterial hypertension in Bulgaria, through the use of quantitative and qualitative measures at the national level." As a secondary aim, she evaluates the obtained data through the prism of rational medicinal use, determining the compliance of the diagnostic and therapeutic strategies in patients with uncomplicated essential arterial hypertension with the treatment standards laid down in the European pharmacotherapeutic guidelines valid for Bulgaria. Achieving these 2 goals becomes possible by solving 9 specific tasks, with detailed descriptions of the methods and materials used for each of them. I am impressed by the correct evaluation of the results and their competent discussion on the basis of publicly available data from the NHIF and NCPRLP registers.

I allowed myself to make a summary table for the 5-year period of the study, based on the data obtained by each year on the number and relative share of patients of the respective types of EAH, the estimated costs of ICD I10 for 1 patient as resp. share of GDP per 1 inhabitant and as a % of the total costs of the NHIF for outpatients, the share of costs for patients with EAH of mono products and combined fixed MP and for the share of uncomplicated EAH. It clearly shows that:

1. The costs paid for the treatment with MP of all patients under home conditions are doubled for the 5-year period from about 800 million BGN in 2017 to 1 billion and 600 million BGN in 2021, and the costs for the treatment of outpatients with EAH decrease from 9.8 million BGN to 7.1 million BGN. The number of patients with EAH also decreased from 1.4 million in 2017 to 1.1 million in 2021 and this reduction of 300,000 is not due to reduced morbidity as a result of preventive measures. I don't buy the concept of a "free market", but why do patients turn to it? The explanation is very simple - because the National Health Insurance Fund reimburses 100% of the costs only for ICD I10, but does not reimburse 100% of the price of prescribed drugs for the treatment of complicated AH. Requiring the patient to receive the MP against a personal document in a narrow time interval creates problems for him and there is another inconvenience for the patient. For example, If MP Renovia 10 mg of Berlin-Chemie, the package of which contains 60 tablets, is prescribed, after the second month the patient must again wait in front of his personal physician's office for a new electronic prescription although the electronic prescription is valid for 3 months. That is why the patient is forced to switch to a generic product with the same INN Lercanidipine 10 mg with 30 tablets in the package so that he does not have to go repeatedly to his GP for prescriptions or if he keeps the prescribed product he has to buy it in the pharmacy at a higher price compared to the agreed price for NHIF.

2. Costs for ICD I10 on average for 1 patient as a % of GDP per 1 resident increased slightly from 0.19% to 0.45%, and as a share of total costs for ambulatory drug treatment decreased from 1.23% to 0.44% for the 5 year period.

3. The number and, accordingly, the share of patients with uncomplicated EAH also decreased for the studied period from 186,000 to 103,000 and, respectively, from 13% to 9% of all patients with EAH in our country, which is why, with this low relative share, it is not surprising that this population of patients has not been the subject of special attention by researchers, as it is quite logical that their attention should be directed to the severe complications of EAH on the cardiovascular and excretory systems, or both.

The conclusions in the dissertation result from the analyzes conducted and the results obtained and are clearly and accurately formulated, with the first three having an ascertaining nature. There are no proposals to the relevant competent authorities and institutions, and I recommend the doctoral student to formulate and address them in order to overcome the identified inconsistencies with the legal requirements in the country.

Basic scientific and scientific-applied contributions. In the most generalized form, in my opinion, the main scientific and applied contributions in the dissertation of mag. Pharm. Stefka Stoyanova Stoyanova can be summarized as follows:

- **Contributions of an original nature:**

1. For the first time, a systematic review of scientific publications was made according to the PRISMA standard for the evaluation of diagnostic and therapeutic strategies in patients with arterial hypertension over a 30-year period in international and national databases.

2. An analysis of the therapeutic strategies in patients with arterial hypertension was carried out by measuring the medicinal usability/in value (BGN), natural (number of packages) and relative (DDD/1 inhabitant/1 year or DDD/1000 women/year) indicators/.

3. A retrospective comparative analysis was conducted between epidemiological and reimbursement data to evaluate the prevention and treatment effectiveness of patients with AH. The study used NHIF reimbursement data to rationalize the drug therapy of patients with AH.

- **A methodical contribution** is the developed original formulation for evaluating the relationships between effective prevention, timely diagnosis, scientifically based treatment, reimbursement, cost-effective therapies and health outcome by measuring drug usability (in quantitative parameters).

- **Scientific-applied and confirmatory contributions:**

1. The study enriches the knowledge of medical specialists (doctors and pharmacists) for the practical application of drug usability and rational drug use in the treatment of socially significant diseases.

2. The study reveals the influence and possibilities, through legally established measures in the pricing and reimbursement systems, to introduce the requirements for rational medicinal use at the national level.

3. The study shows the existence of some regulatory problems in the confirmation and implementation in real practice of the pharmacotherapeutic guidelines by the national competent authorities for the treatment of various groups of diseases, including and AH.

The dissertation enriches the Bulgarian pharmaceutical literature and gives rise to ideas for new similar future studies on the subject. The doctoral student presents a well-formed dissertation, which is structured correctly and synthetically reflects the most important results of studies in accordance with the set goals and objectives. The abstract contains a brief description of the main studies, conclusions and contributions of the dissertation.

Reflection of the candidate's scientific publications in the specialized scientific literature

The following are presented on the topic of the dissertation **2** publications published in scientific publications, referenced and indexed in world-renowned databases of scientific information (**Arch Balk Med Union and Journal of Generic Medicines**) and **5** publications and reports published in non-refereed peer-reviewed journals or published in edited collective volumes. Out of a total of 7 publications and reports presented, the doctoral student is the first author in 4 of them.

The reference of the doctoral student Stefka Stoyanova Stoyanova for the fulfillment of the minimum national requirements under Article 26 of the ZRASRB includes 117.80 points, , i.e. **she exceeds them.**

Conclusion. The PhD student M. Pharm. Stefka Stoyanova Stoyanova presents a dissertation work dedicated to a current and significant problem for our health care. The results of the research are published in the specialized literature and reported on pharmaceutical scientific forums. The dissertation is an original medico-social analysis and contains scientific and applied scientific results that represent a significant contribution to pharmaceutical science. It shows that the candidate has in-depth theoretical knowledge of the scientific specialty and abilities for independent scientific research. The dissertation fulfills all the requirements of LDASRB, RALDASRB and the Regulations for the terms and conditions for acquiring scientific degrees and occupying academic positions in SU "St. Kliment Ohridski" for the acquisition of the ESD "doctor". I give my positive assessment of the dissertation and fully convinced that I will support the awarding of the ESD "Doctor" in Pharmacy to Stefka Stoyanova Stoyanova in the doctoral program "Social Medicine and Organization of Health Care and Pharmacy" by voting "Yes".

29.11.2023r.
Sofia

Reviewer:.....

/prof. ZL. Dimitrova, DSc./